IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of

David J. Bova — Group Art Unit: 1502

Serial No: 08/960,557 — Examiner: L.Channavajjala

Filed: Oct. 31, 1997

For: METHODS FOR TREATING HYPERLIPIDEMIA WITH INTERMEDIATE RELEASE NICOTINIC ACID FORMULATIONS HAVING UNIQUE BIOPHARMACEUTICAL RELEASE CHARACTERISITCS

DECLARATION UNDER 37 CFR §1.131

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, David J. Bova, state and declare that:

1. I am the named inventor of the above-captioned application, which is a continuation-in-part application of U.S. serial No. 08/814,974, filed on March 6, 1997, now Patent No. 6,129,930, which is a continuation in part of 08/368,378 filed on Jan. 14, 1995, now Patent No. 6,080,428, which is a continuation-in-part of 08/124,392, filed September 20, 1993 ("the parent application"), now abandon.

2. In the office action of June 14, 2007, the examiner maintained a rejection of claims 29-36 and 38-61 under 35 USC §102(e), as being anticipated by O'Neill *et al.*, U.S. Patent No. 5,268,181 (1993), which was filed on June 29, 1992.

3. As Vice President of Research and Development for KOS Pharmaceuticals, Inc., I prepared protocol 89-04 to compare the effect on serum lipids of sustained release nicotinic acid that was administered once-a-day (either in the evening or at night) or twice-a-day during the day. KOS Pharmaceuticals, Inc., the assignee of the above-captioned application, sponsored the study, and I monitored the performance and conduct of the study.

4. The KOS Pharmaceuticals 89-04 study was conducted with male and female patients having total cholesterol levels greater than 260 mg/dl. The selection criterion for

patients was based upon the report of an expert panel of the National Cholesterol Education Program, which was published in *Arch. Intern. Med. 148*: 36 (1988). A copy of the report is attached to this declaration as Exhibit 1. The panel concluded that individuals with blood cholesterol levels $\geq$ 240 mg/dl should be classified as having "high" cholesterol levels. Therefore, the patients included in the KOS Pharmaceuticals study were considered to have high cholesterol levels, and they were classified as hyperlipidemics. Accordingly, the study was performed to determine a method of treating hyperlipidemia in hyperlipidemics comprising the administration of an effective amount of nicotinic acid once per day in the evening or at night, as stated in claim 1. Relevant sections of the 89-04 study protocol were attached as Exhibit A in my declaration of August 17, 1995.

5. The results of the KOS Pharmaceuticals 89-04 study were disclosed in the above-captioned application and in the parent application in Table II. Group A patients were from the 89-04 study. The relevant pages of the parent application are attached to this declaration as Exhibit 2. Briefly, we found that the mean blood cholesterol level at baseline and prior to treatment was 282.2 mg/dl. In the group that received nicotinic acid once per day at night, the mean blood cholesterol level decreased 12.5% to 246.9 mg/dl. Analysis of the clinical data revealed that this decrease in blood cholesterol was highly statistically significant. Thus, the administration of a sustained release formulation of nicotinic acid (once per day in the evening or at night) is an effective treatment for hyperlipidemia.

6. The KOS Pharmaceuticals 89-04 study began in 1990, and the study was conducted in the United States. Data analyses were also performed in the United States. Although the last visit for the last patient took place on March 20, 1991, statistical analyses were performed each time data was entered into the database. Exhibit 3 presents an analysis of data that had been collected by December 31, 1990, and demonstrates that a statistically significant reduction in total cholesterol was observed by that time. Exhibit 3 also includes copies of medical documents containing the clinical data used in the analysis.

7. As Vice President of Research and Development for KOS Pharmaceuticals, Inc., I also prepared protocol 91-02 to determine the efficacy of 1500mg dose of Niaspan

given once-a-day at bedtime for the reduction of elevated lipid levels in patients with type IIa hyperlipoproteinemia. KOS Pharmaceuticals, Inc., the assignee of the above-captioned application, sponsored the study, and I monitored the performance and conduct of the study.

8. The KOS Pharmaceuticals 91-02 study was conducted with male and female patients with hyperlipoproteinemia. The selection criterion for patients was based upon the report of an expert panel of the National Cholesterol Education Program, which was published in *Arch. Intern. Med. 148*: 36 (1988).

9. The results of the KOS Pharmaceuticals 91-02 study were disclosed in the above-captioned application and in the parent application in Table II. Group B patients were from the 91-02 study. The relevant pages of the parent application are attached to this declaration as Exhibit 2. Briefly, we found that the mean blood cholesterol level at baseline and prior to treatment was 296.9 mg/dl. After treatment the mean blood cholesterol level decreased 8.1% to 271.4 mg/dl.

10. The KOS Pharmaceuticals 91-02 study began in 1991, and the study was conducted in the United States. Data analyses were also performed in the United States. Although the last visit for the last patient took place on October 4, 1991, statistical analyses were performed each time data was entered into the database.

11. As described below, the KOS Pharmaceuticals studies verified a method of treating hyperlipidemia in a hyperlipidemic comprising the administration of nicotinic acid once per day in the evening or at night. Moreover, nicotinic acid was administered to patients in combination with a pharmaceutically acceptable carrier. Accordingly, the invention presently described in claim 1 was conceived and reduced to practice in the United States prior to June 29, 1992, the filing date of the O'Neill patent.

12. In the KOS Pharmaceuticals studies, patients received nicotinic aeid in the form of sustained release tablets containing nicotinic acid, hydroxypropylmethylcellulose, povidone and stearic acid, as shown in Table I of both the above-captioned application and the parent application. See page 6 of the parent application, which is attached to this declaration as Exhibit 4. Povidone is also known as "polyvinylpyrrolidone." We included stearic acid in the formulation of the study as a lubricating agent. See, for example, the parent application at page 5, fourth full paragraph. Accordingly, the use of a formulation

for treating hyperlipidemia that comprises nicotinic acid, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the lubricant, stearic acid, antedates the filing date of the O'Neill patent.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: December 12, 2007

David J. Bova

Exhibit 1

Special Article

Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

The Expert Panel

• **This report of an expert panel of the National Cholesterol Education Program provides new guidelines for the treatment of high blood cholesterol in adults 20 years of age and over. Total cholesterol levels are classified as follows: <200 mg/dL—"desirable blood cholesterol"; 200 to 239 mg/dL—borderline–high blood cholesterol; ≥240 mg/dL—high blood cholesterol. The guidelines detail which patients should go on to have lipoprotein analysis, and which should receive cholesterol-lowering treatment on the basis of their low density lipoprotein (LDL)–cholesterol levels and status with respect to other coronary heart disease risk factors. Dietary therapy is the primary cholesterol-lowering treatment. The report specifies the LDL-cholesterol levels at which dietary therapy should be started and the goals of therapy, and provides detailed guidance on the nature of the recommended dietary changes. If, after six months of intensive dietary therapy, LDL-cholesterol exceeds specified levels, drug treatment should be considered.**

(*Arch Intern Med* 1988;148:36-49)

OVERVIEW AND SUMMARY

Increased blood cholesterol levels, or, more specifically, increased levels of low density lipoprotein (LDL)–cholesterol, are causally related to an increased risk of coronary heart disease (CHD). Coronary risk rises progressively with an increase in cholesterol level, particularly when cholesterol levels rise above 200 mg/dL (for Système International [SI] conversions throughout text, refer to Appendix I, Table 1). There is also substantial evidence that lowering total and LDL-cholesterol levels will reduce the incidence of CHD.

Two approaches can be used to lower blood cholesterol levels. The first is the subject of this report: a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal here is to establish criteria that define the candidates for medical intervention and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time. The second approach, the population (public health) strategy, aims to shift the distribution of cholesterol levels in the entire population to a lower range. These two approaches are complementary and, together, represent a coordinated strategy aimed at reducing cholesterol levels and coronary risk.

Case finding: Initial Classification by Total Blood Cholesterol (Table 1)

Serum total cholesterol should be measured in all adults 20 years of age and over at least once every five years; this measurement may be made in the nonfasting state. Levels below 200 mg/dL are classified as "desirable blood cholesterol," those 200 to 239 mg/dL as "borderline–high blood cholesterol," and those 240 mg/dL and above as "high blood cholesterol." The cutpoint that defines high blood cholesterol (240 mg/dL) is a value above which risk of CHD rises steeply, and corresponds approximately to the 75th percentile for the adult US population. The cutpoints recommended in this report are uniform for adult men and women of all ages.

Accepted for publication Sept 28, 1987.

From the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, Bethesda, Md.

Reprint requests to Coordinator, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, Bldg 31, Room 4A 05, Bethesda, MD 20892 (Dr Cleeman).

Table 1.—Initial Classification and Recommended Followup Based on Total Cholesterol*

Classification, mg/dL	
<200	Desirable blood cholesterol
200 to 239	Borderline–high blood cholesterol
≥240	High blood cholesterol
Recommended followup	
Total cholesterol, <200 mg/dL	Repeat within five years
Total cholesterol, 200-239 mg/dL	
Without definite CHD or two other CHD risk factors (one of which can be male sex)	Dietary information and recheck annually
With definite CHD or two other CHD risk factors (one of which can be male sex)	Lipoprotein analysis; further action based on LDL-cholesterol level
Total cholesterol ≥240 mg/dL	

*CHD indicates coronary heart disease; LDL, low density lipoprotein.

Table 2.—Classification and Treatment Decisions Based on LDL-Cholesterol*

Classification, mg/dL		
<130	Desirable LDL-cholesterol	
130 to 159	Borderline-high-risk LDL-cholesterol	
≥160	High-risk LDL cholesterol	
	Initiation Level, mg/dL	Minimal Goal, mg/dL
Dietary treatment		
Without CHD or two other risk factors†	≥160	<160‡
With CHD or two other risk factors†	≥130	<130§
Drug treatment		
Without CHD or two other risk factors†	≥190	<160
With CHD or two other risk factors†	≥160	<130

*LDL indicates low density lipoprotein; CHD, coronary heart disease.
†Patients have a lower initiation level and goal if they are at high risk because they already have definite CHD, or because they have any two of the following risk factors: male sex, family history of premature CHD, cigarette smoking, hypertension, low high density lipoprotein (HDL)-cholesterol, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity.
‡Roughly equivalent to total cholesterol level of <240 mg/dL‡ or <200 mg/dL.
§As goals for monitoring dietary treatment.

Along with cholesterol testing, all adults should also be evaluated for the presence of other CHD risk factors, including hypertension, cigarette smoking, diabetes mellitus, severe obesity, and a history of CHD in the patient or of premature CHD in family members. Patients with other risk factors should be given other forms of preventive care as appropriate.

Patients with desirable blood cholesterol levels (<200 mg/dL) should be given general dietary and risk reduction educational materials, and advised to have another serum cholesterol test within five years. Patients with cholesterol levels 200 mg/dL or greater should have the value confirmed by repeating the test; the average of the two test results is then used to guide subsequent decisions. Patients with high blood cholesterol (≥240 mg/dL) should undergo lipoprotein analysis, as should those with a borderline–high blood cholesterol (200 to 239 mg/dL) who are at high risk because they have definite CHD or two other CHD risk factors; in this report male sex is considered a risk factor for the purpose of estimating risk status. Patients with confirmed borderline–high blood cholesterol levels who do not have CHD or two other risk factors do not need further evaluation and active medical therapy; they should be given the dietary information designed for the general population and reevaluated at one year.

Some experts believe that patients in the borderline–high blood cholesterol group who have one other risk factor (eg, hypertension), or who are of younger age (20 to 39 years), should also undergo lipoprotein analysis. Although this is not recommended here as a general approach for the borderline–high blood cholesterol group, it is clear that individualized clinical judgment and patient management is appropriate for this group.

Deciding to Treat: Classification by LDL-Cholesterol (Table 2)

Once someone is identified as requiring lipoprotein analysis, the focus of attention should shift from total cholesterol to LDL-cholesterol. The ultimate objective of case finding and screening is to identify individuals with elevated LDL-cholesterol levels. Similarly, the specific goal of treatment is to lower LDL-cholesterol levels. Hence, the level of LDL-cholesterol will serve as the key index for clinical decision making about cholesterol-lowering therapy.

Lipoprotein analysis involves measurement of the fasting levels of total cholesterol, total triglyceride, and high density lipoprotein (HDL)-cholesterol. From these values, LDL-cholesterol is calculated as follows: LDL-Cholesterol = Total Cholesterol – HDL-Cholesterol – (Triglyceride/5).

Levels of LDL-cholesterol of 160 mg/dL or greater are classified as "high-risk LDL-cholesterol," and those 130 to 159 mg/dL as "borderline–high-risk LDL-cholesterol." Patients with high-risk LDL-cholesterol levels, and those with borderline-high-risk LDL-cholesterol levels who have definite CHD or two other risk factors (one of which can be male sex), should have a complete clinical evaluation and then begin cholesterol-lowering treatment. A basic principle adopted in this report is that the presence of other risk factors or definite CHD warrants initiating treatment at lower LDL-cholesterol levels and the setting of lower LDL-cholesterol treatment goals. In this scheme, a low level of HDL-cholesterol (below 35 mg/dL) is considered another risk factor (like hypertension) that will affect the assessment of overall coronary risk, and, in this way, influence clinical decisions about treatment.

The clinical evaluation should include a complete history, physical examination, and basic laboratory tests. This workup will aim to determine whether the high LDL-cholesterol level is secondary to another disease or a drug, and whether or not a familial lipid disorder is present. The patient's total coronary risk and clinical status, as well as age and sex, should be considered in developing a cholesterol-lowering treatment program.

Dietary Treatment

Treatment begins with dietary therapy. The minimal goals of therapy are to lower LDL-cholesterol to levels below the cutpoints for initiating therapy, ie, to below 160 mg/dL, or to below 130 mg/dL if definite CHD or two other CHD risk factors are present. Ideally, even lower levels of LDL-cholesterol should be attained, if possible, to achieve a further reduction in risk.

Although the goal of therapy is to lower the LDL-

cholesterol level, most patients can be managed during dietary therapy on the basis of their total cholesterol levels. This has the advantage of avoiding the additional costs and the need for a fasting blood specimen involved in the measurement of LDL-cholesterol levels. Serum total cholesterol levels of 240 and 200 mg/dL correspond roughly to LDL-cholesterol levels of 160 and 130 mg/dL, respectively. Thus, the monitoring goals during dietary therapy are to lower the serum total cholesterol level to below 240 mg/dL for patients with an LDL-cholesterol goal of <160 mg/dL, or to below 200 mg/dL for patients with an LDL-cholesterol goal of <130 mg/dL.

The general aim of dietary therapy is to reduce elevated cholesterol levels while maintaining a nutritionally adequate eating pattern. Dietary therapy should occur in two steps, the Step-One and Step-Two Diets, that are designed to progressively reduce intakes of saturated fatty acids and cholesterol, and to promote weight loss in patients who are overweight by eliminating excess total calories. The Step-One Diet should be prescribed and explained by the physician and his or her staff. This diet involves an intake of total fat less than 30% of calories, saturated fatty acids less than 10% of calories, and cholesterol less than 300 mg/d. The Step-Two Diet, used if the response to the Step-One Diet is insufficient, calls for a further reduction in saturated fatty acid intake to less than 7% of calories and in cholesterol to less than 200 mg/d. The Step-One Diet calls for the reduction of the major and obvious sources of saturated fatty acids and cholesterol in the diet; for many patients this can be achieved without a radical alteration in dietary habits. The Step-Two Diet requires careful attention to the whole diet so as to reduce intake of saturated fatty acids and cholesterol to a minimal level compatible with an acceptable and nutritious diet. Involvement of a registered dietitian is very useful, particularly for intensive dietary therapy such as the Step-Two Diet.

After starting the Step-One Diet, the serum total cholesterol level should be measured and adherence to the diet assessed at four to six weeks and at three months. If the total cholesterol monitoring goal is met, then the LDL-cholesterol level should be measured to confirm that the LDL goal has been achieved. If this is the case, the patient enters a long-term monitoring program, and is seen quarterly for the first year and twice yearly thereafter. At these visits total cholesterol levels should be measured, and dietary and behavior modifications reinforced.

If the cholesterol goal has not been achieved with the Step-One Diet, the patient should generally be referred to a registered dietitian. With the aid of the dietitian, the patient should progress to the Step-Two Diet, or to another trial on the Step-One Diet (with progression to the Step-Two Diet if the response is still not satisfactory). On the Step-Two Diet, total cholesterol levels should again be measured and adherence to the diet assessed after four to six weeks and at three months of therapy. If the desired goal for total cholesterol (and for LDL-cholesterol) lowering has been attained, long-term monitoring can begin. If not, drug therapy should be considered. A minimum of six months of intensive dietary therapy and counseling should usually be carried out before initiating drug therapy; shorter periods can be considered in patients with severe elevations of LDL-cholesterol (>225 mg/dL) or with definite CHD. Drug therapy should be added to dietary therapy, and not substituted for it.

Drug Treatment

Drug therapy should be considered for an adult patient who, despite dietary therapy, has an LDL-cholesterol level of 190 mg/dL or higher if the patient does not have definite CHD or two other risk factors (one of which can be male sex). If the patient does have definite CHD or two other risk factors, then drug therapy should be considered at LDL-cholesterol levels of 160 mg/dL or higher. The goals of drug therapy are the same as those of dietary therapy: to lower LDL-cholesterol to below 160 mg/dL, or to below 130 mg/dL if definite CHD or two other risk factors are present. These are minimal goals; if possible, considerably lower levels of LDL-cholesterol should be attained.

Individualized clinical judgment is needed for patients who do not meet these criteria for drug therapy, but have not attained their minimal goals on dietary therapy. These patients include those without definite CHD or two other risk factors whose LDL-cholesterol levels remain in the range of 160 to 190 mg/dL, and patients with CHD or two other risk factors whose LDL-cholesterol levels remain in the range of 130 to 160 mg/dL, on adequate dietary therapy. In general, maximal efforts should be made in this group to achieve lower cholesterol levels and lower CHD risk by means of nonpharmacologic approaches. Consideration should also be given to the use of low doses of bile acid sequestrants in these patients, especially in males. Moreover, many experts feel that patients with definite CHD should receive drug therapy if their minimal LDL-cholesterol goal (<130 mg/dL) has not been reached.

The drugs of first choice are the bile acid sequestrants (cholestyramine, colestipol) and nicotinic acid. Both cholestyramine and nicotinic acid have been shown to lower CHD risk in clinical trials, and their long-term safety has been established. However, these drugs require considerable patient education to achieve effective adherence. Nicotinic acid is the preferred drug in patients with concurrent hypertriglyceridemia (triglyceride levels ≥250 mg/dL), because bile acid sequestrants tend to increase triglyceride levels.

A new class of drugs, to be considered after the bile acid sequestrants and nicotinic acid, is the 3-hydroxy-3-methylglutaryl coenzyme-A (HMG CoA) reductase inhibitors (e.g., lovastatin). These drugs are very effective in lowering LDL-cholesterol levels, but their effects on CHD incidence and their long-term safety have not yet been established.

Other available drugs include gemfibrozil, probucol, and clofibrate. Gemfibrozil and clofibrate are fibric acid derivatives; they are primarily effective for lowering elevated triglyceride levels, but are not approved by the Food and Drug Administration for routine use in lowering cholesterol levels.

After starting drug therapy, the LDL-cholesterol level should be measured at four to six weeks, and then again at three months. If the response to drug therapy is adequate (ie, the LDL-cholesterol goal has been achieved), then the patient should be seen every four months, or more frequently when drugs requiring closer followup are used, in order to monitor the cholesterol response and possible side effects of therapy. For long-term monitoring, serum total cholesterol alone can be measured at most follow-up visits, with lipoprotein analysis (and LDL-cholesterol estimation) carried out once a year.

If the response to initial drug therapy is not adequate, the patient should be switched to another drug, or to a combination of two drugs. The combination of a bile acid sequestrant with either nicotinic acid or an HMG CoA reductase inhibitor has the potential of lowering LDL-cholesterol levels by 40% to 50% or more. The combination of colestipol and nicotinic acid has been shown to beneficially influence coronary atherosclerotic lesions. For most patients, the judicious use of one or two drugs should be

able to provide an adequate LDL-cholesterol–lowering effect.

Drug therapy is likely to continue for many years, or for a lifetime. Hence, the decision to add drug therapy to the regimen should be made only after vigorous efforts at dietary treatment have not proven sufficient. The patient must be well informed about the goals and side effects of medication and the need for long-term commitment. In the ideal treatment setting, the management of high-risk cholesterol levels would call on the expertise of a variety of professionals. The office nurse or physician's assistant can help greatly in promoting adherence to dietary and drug therapy. A registered dietitian can be of great value in dietary therapy. The pharmacist can help to provide counseling and promote adherence with drug therapy. Consultation with a lipid specialist is useful for patients with unusually severe, complex, or refractory lipid disorders.

CLASSIFICATION, PREVALENCE, DETECTION, AND EVALUATION

Background and Introduction

This report provides practical guidelines for clinicians to use in measuring and reducing blood cholesterol in adult patients. (This report addresses patients 20 years of age and above; a separate panel will provide guidelines for children and adolescents.) The report adds a more specific set of recommendations to basic policies set forth by previous bodies, notably the National Institutes of Health (NIH) Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease.[1] While it is recognized that approaches for modifying the cholesterol levels in whole population groups are important, this report focuses on caring for individual patients.

Basic Description of Lipids and Lipoproteins.—Cholesterol is a fatlike substance (lipid) that is a key component of cell membranes and a precursor of bile acids and steroid hormones. Cholesterol travels in the circulation in spherical particles containing both lipids and proteins called lipoproteins. The cholesterol level in blood plasma is determined partly by inheritance and partly by the fat and cholesterol content of the diet. Other factors such as obesity and physical inactivity may also play a role.

Three major classes of lipoproteins can be measured in the serum of a fasting individual: very low density lipoproteins (VLDL), LDL, and HDL. The LDL are the major atherogenic class, and, typically, contain 60% to 70% of the total serum cholesterol. The HDL usually contain 20% to 30% of the total cholesterol, and their levels are inversely correlated with risk for CHD. The VLDL, which are largely composed of triglycerides, contain 10% to 15% of the total serum cholesterol.

Because most of the cholesterol in the serum is found in the LDL, the concentration of total cholesterol is closely correlated with the concentration of LDL-cholesterol. Thus, while LDL-cholesterol is the actual target of cholesterol-lowering efforts, total cholesterol can be used in its place in the initial stages of evaluating a patient's serum lipids. Testing for serum total cholesterol is more available and less expensive and does not require that the patient be fasting. On the other hand, LDL-cholesterol offers more precision as a risk factor and is therefore preferred for clinical decisions about interventions to lower blood cholesterol, especially in patients who may be candidates for cholesterol-lowering drugs.

Rationale for Intervention.—*The Evidence That LDL-Cholesterol Is a Cause of CHD.*—The conclusion that high levels of LDL-cholesterol are a cause of coronary atherosclerosis and produce an increased risk of CHD comes from the congruent results of many studies.

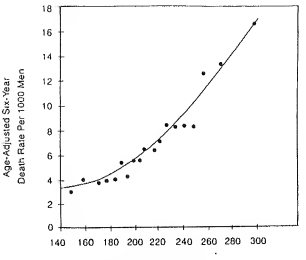

Fig 1.—Relationship of serum cholesterol to coronary heart disease (CHD) death in 361 662 men 35 to 57 years of age during an average followup of six years. Each point represents median value for 5% of the population.[3] Key points are as follows: (1) risk increases steadily, particularly above levels of 200 mg/dL; and (2) the magnitude of the increased risk is large, fourfold in the top 10% as compared with the bottom 10%.

EPIDEMIOLOGIC EVIDENCE.—A large body of epidemiologic evidence supports a direct relationship between the level of serum total and LDL-cholesterol and the rate of CHD.[2-4] Comparisons among various populations throughout the world reveal a direct correlation between serum cholesterol levels and CHD rates. People who have migrated to a country that has a higher average serum cholesterol level gradually acquire the dietary habits, serum cholesterol level, and CHD rates of their new country. Prospective studies of the individuals within a population have uniformly shown that serum cholesterol levels predict the future occurrence of CHD morbidity and mortality. This association is continuous throughout the range of cholesterol levels in the population (Fig 1).[5,6] At higher levels of serum cholesterol, the relationship becomes particularly strong. For persons with cholesterol values in the top 10% of the population distribution, the risk of CHD mortality is four times as high as the risk in the bottom 10% of the population.

GENETIC AND PHYSIOLOGIC EVIDENCE.—Premature CHD can result from high LDL-cholesterol levels even in the absence of any other risk factors.[7] This is most clearly demonstrated in children who have the rare homozygous familial hypercholesterolemia, a disorder characterized by the absence of the specific cell-surface receptors that normally remove LDL from the circulation.[8] The LDL-cholesterol levels can be as high as 1000 mg/dL, and severe atherosclerosis and CHD can develop during the first two decades of life. Patients with the more common heterozygous form of familial hypercholesterolemia and partial deficiencies of LDL-receptor function commonly develop premature CHD in the middle decades of life.

ANIMAL MODEL EVIDENCE.—Animal models have demonstrated important relationships between LDL-cholesterol and atherosclerosis.[9] Many animal species (including monkeys and baboons) develop atherosclerosis when fed

diets that raise their serum cholesterol levels. These hypercholesterolemic animals develop intimal lesions that progress from fatty streaks to complicated ulcerated plaques resembling those of human atherosclerosis. Severe atherosclerosis in monkeys regresses when the blood cholesterol is lowered substantially for an extended period by diet or drugs. These studies thus support a causal relationship between LDL-cholesterol and atherosclerosis, and suggest that this process may be reversible under some circumstances.

The Evidence That Reducing LDL-Cholesterol Levels Will Prevent CHD.—The evidence noted above from epidemiologic, genetic, and animal investigations strongly supports a causal link between elevated serum cholesterol levels and CHD. In addition, clinical trials have shown that this risk can be altered—that lowering LDL-cholesterol in men with high levels decreases the incidence of CHD.

The issue of whether lowering LDL-cholesterol levels by dietary and drug interventions can reduce the incidence of CHD has been addressed in more than a dozen randomized clinical trials. One of the largest, the Coronary Primary Prevention Trial, which compared the cholesterol-lowering drug cholestyramine with a placebo, produced statistically significant reductions in LDL-cholesterol levels and in the incidence of CHD.[10] An aggregate analysis that pools the results of serum cholesterol-lowering trials confirms an effect on CHD incidence. Moreover, the Coronary Drug Project has shown a significant decrease in overall mortality (compared with the placebo group) in a long-term followup of men treated with nicotinic acid after myocardial infarction.[11] In addition, a recent angiographic study showed that cholesterol-lowering dietary and drug therapy slowed the progression and produced regression of coronary atherosclerosis in men with bypass grafts.[12]

In summary, these findings support the conclusion that lowering total and LDL-cholesterol levels will reduce the subsequent incidence of CHD events. Moreover, the pooled analysis of clinical trial findings suggests that intervention is as effective in secondary prevention (preventing recurrent myocardial infarction and death in patients who have had a heart attack) as it is in primary prevention. The direct evidence from clinical trials is strongest in middle-aged men with high initial cholesterol levels. However, the complete set of evidence, including the epidemiologic observations and animal experiments, strongly supports the generalization that reducing total and LDL-cholesterol levels is also likely to reduce CHD incidence in younger and older men, in women, and in individuals with more moderate elevations of cholesterol.

The Magnitude of the Reduction in CHD.—Epidemiologic studies and clinical trials are remarkably consistent in supporting the projection that for individuals with serum cholesterol levels initially in the 250 to 300 mg/dL range, each 1% reduction in serum cholesterol level yields approximately a 2% reduction in CHD rates.[13] Thus, for example, it is reasonable to estimate that a 10% to 15% reduction in serum cholesterol level resulting from the diets recommended in this report should reduce CHD risk by 20% to 30%.

The *absolute magnitude* of these benefits will probably be greatest in patients who are at high risk because of the presence of other risk factors, such as cigarette smoking and hypertension. This concept is illustrated in Table 3 using data from the Multiple Risk Factor Intervention Trial (MRFIT). Among nonsmokers with normal blood pressure, the risk of CHD death per 1000 men in the six years of observation was 6.4 in the top quintile of serum cholesterol and 1.6 in the bottom quintile, a difference of 4.8. Among smokers with hypertension, the comparable figures were 21.4 and 6.3, a difference of 15.1. Thus, an intervention that lowered cholesterol levels from the highest to the lowest quintile should have three times the benefit (15 vs five deaths prevented per thousand persons) when applied to men who have the other two risk factors (assuming no change in those other risk factors). These risk relationships are the basis for recommending lower cholesterol cutpoints and goals for treating patients who, for other reasons (in addition to cholesterol), are at high risk for developing CHD.

Table 3.—Coronary Heart Disease Deaths per 1000 in Men 35 to 57 Years of Age With an Average Followup of Six Years According to Serum Cholesterol Quintile and Presence or Absence of Other Risk Factors.[14] The Difference in Absolute Risk in the Highest vs the Lowest Quintile of Serum Cholesterol Is Greater in Patients Who Are at High Risk for Other Reasons.

Serum Cholesterol Quintile, mg/dL	Normotensive Nonsmoker	Hypertensive Smoker
<182	1.6	6.3
182 to 202	2.5	10.0
203 to 220	2.7	15.5
221 to 244	3.8	16.8
≥245	6.4	21.4

Classification of Patients by Total and LDL-Cholesterol Levels.—Population distributions for serum total cholesterol and LDL-cholesterol levels in the United States are provided in Appendix 1, Tables. To convert serum values to plasma, multiply by 0.97. To convert cholesterol values in milligrams per deciliter to millimoles per liter, multiply by 0.02586. To convert triglyceride values in milligrams per deciliter to millimoles per liter, multiply by 0.01129.

The classification system (Fig 2) begins with measurement of the total cholesterol level. Serum is most frequently used for this measurement, and cholesterol levels in this report are stated as serum values. (Cholesterol levels can also be measured on plasma. If, as is customary, ethylenediaminetetraacetic acid [EDTA] is used as an anticoagulant, the results should be multiplied by 1.03 to arrive at the serum equivalent.) Levels below 200 mg/dL are classified as "desirable blood cholesterol," those 200 to 239 mg/dL as "borderline-high blood cholesterol," and those 240 mg/dL and above (corresponding to approximately the top 25% of the entire adult population 20 years of age and above) as "high blood cholesterol."

Patients with high blood cholesterol need additional evaluation and are further classified for the purposes of clinical decisions about possible dietary and drug treatment by performing lipoprotein analysis and estimating the more specific determinant of CHD risk, the LDL-cholesterol level. Levels of LDL-cholesterol that are 160 mg/dL and above are classified as "high-risk LDL-cholesterol."

Because the relationship between serum cholesterol level and CHD is a continuous and steadily increasing one (Fig 1), these cutpoints are necessarily somewhat arbitrary. However, this is also true of other risk factors, such as blood pressure, and the success of basing clinical decisions on whether or not a patient is classified as hypertensive indicates the value of establishing cutpoints for clinical decisions. The 240 mg/dL cutpoint for total serum cholesterol is a level at which CHD risk is almost double that at 200 mg/dL, and is rising steeply. Patients with cholesterol levels at or above this cutpoint have sufficiently high risk

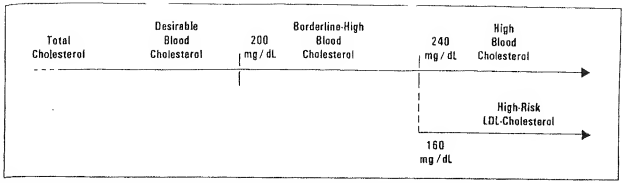

Fig 2.—Classification by total and low density lipoprotein (LDL)–cholesterol levels. Key points are as follows: (1) serum cholesterol is used for initial classification; (2) low density lipoprotein–cholesterol is used for those with high levels.

to warrant more detailed evaluation and possible treatment.

Other Risk Factors for CHD.—Coronary heart disease is a disease of multifactorial etiology, and other risk factors should also be considered in preventive medical efforts. These include modifiable factors like hypertension and cigarette smoking, which are appropriate targets for intervention efforts. (Assistance in intervention efforts aimed at hypertension and cigarette smoking may be obtained from two National Heart, Lung, and Blood Institute publications: "The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" [to be updated in 1988]; and "Clinical Opportunities for Smoking Intervention—A Guide for the Busy Physician.") Everyone tested for blood cholesterol should also be examined for other risk factors (Table 4), and intervention should be undertaken as appropriate. All patients should receive educational materials that describe general dietary and life-style approaches to reducing the risk of CHD. (These materials may be obtained from a variety of sources—see the list in the National Cholesterol Education Program publication "Cholesterol Resources for the Physician.") Advice to quit smoking is particularly important because it has the potential not only to reduce CHD risk by 50%, but also to prevent cancer and chronic lung disease.

In addition to being candidates for intervention, these modifiable factors increase the absolute level of CHD risk and thereby enhance the potential value of reducing cholesterol levels. This is also true for the fixed risk factors like older age, male sex, family history of premature CHD, and CHD in the patient. Two other lipid and lipoprotein factors that have a bearing on CHD, HDL-cholesterol and triglyceride, are not dealt with in this report as direct targets for intervention but enter into clinical decisions in ways that are discussed in the sections that follow and in Appendix II.

The Patient-Based Approach and the Population-Based Approach.—The 1984 Consensus Conference and other groups have recommended two major strategies for preventing CHD by lowering blood cholesterol levels.[1,2,13] One is the subject of this report: a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal here is to establish total and LDL-cholesterol cutpoints that define the candidates for medical intervention, and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time.

The other strategy is the population-based approach that seeks to lower the mean serum cholesterol level by modifying the dietary habits of the entire population. This strategy has the general goal of lowering the serum cholesterol levels of the population at large.

These two strategies are complementary, not competitive, and the National Cholesterol Education Program is considering both in the development of its activities. This report is the product of an expert panel focused on the patient-based approach. Another panel is charged with examining the scientific evidence and making recommendations for the population-based approach.

The Importance of a Multidisciplinary Team Approach.—This report presents guidelines for interventions that are partly the responsibility of the physicians, dietitians, nurses, pharmacists, and other health professionals who must work together as a team to decide on the best approach for testing and treating each patient, and for implementing and following up these recommendations. The interventions are also the responsibility of the patient, for whom the challenge is to make the dietary and other life-style changes that are needed for successful reduction of CHD risk.

Table 4.—Risk Status Based on Presence of CHD Risk Factors Other Than LDL-Cholesterol

The patient is considered to have a high risk status if he or she has one of the following:
Definite CHD; the characteristic clinical picture and objective laboratory findings of either:
Definite prior myocardial infarction, or
Definite myocardial ischemia, such as angina pectoris
Two other CHD risk factors;
Male sex*
Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in a parent or sibling)
Cigarette smoking (currently smokes more than ten cigarettes per day)
Hypertension
Low HDL-cholesterol concentration (below 35 mg/dL confirmed by repeated measurement)
Diabetes mellitus
History of definite cerebrovascular or occlusive peripheral vascular disease
Severe obesity (≥30% overweight)

*Male sex is considered a risk factor in this scheme because the rates of CHD are three to four times higher in men than in women in the middle decades of life and roughly two times higher in the elderly. Hence, a man with one other CHD risk factor is considered to have a high-risk status, whereas a woman is not so considered unless she has two other CHD risk factors.

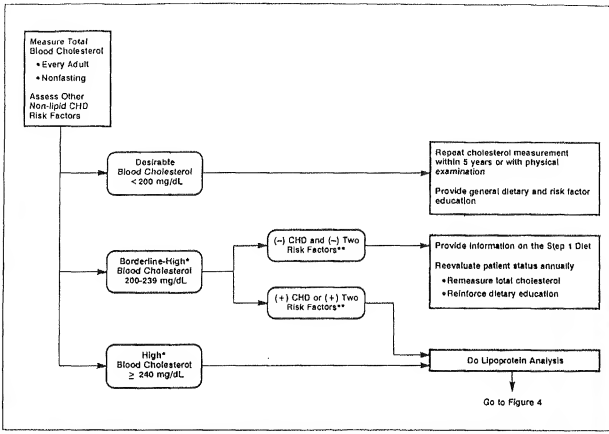

Fig 3.—Initial classification based on total cholesterol. CHD indicates coronary heart disease; asterisk, must be confirmed by obtaining repeated measurements and then using the average value; double asterisks, one of which can be male sex (Table 4).

Detection and Evaluation

Who Should Be Tested.—The total cholesterol level should be measured in all adults 20 years of age and over at least once every five years. Although screening programs that have the specific purpose of inviting the public to receive this test can be used (provided that care is taken to assure that the screening determination is accurate and that there is appropriate followup for further tests and treatment), the usual approach is through case finding. Case finding is defined as testing the cholesterol level as part of any medical examination.

Classification of Patients.—*Initial Classification Based on Total Cholesterol Level.*—The schedule for evaluation and followup of serum cholesterol concentration is shown in Fig 3. The schedule begins with measurement of the nonfasting serum total cholesterol level and an assessment of other nonlipid risk factors including blood pressure, smoking, and history of CHD in the patient or of premature CHD in family members. The presence of a high cholesterol level is confirmed with a second test and then the fasting LDL-cholesterol level is measured in order to provide a more precise estimate of risk on which to base treatment. Patients should be asked not to change their eating habits during this series of baseline tests.

Patients with a *desirable blood cholesterol* level at this initial test (<200 mg/dL) should be given advice and educational materials on the diet recommended for the general population and advised to have another serum cholesterol test within five years. As with all patients, these individuals should also have been evaluated for hypertension, cigarette smoking, and other risk factors, and should be given other forms of preventive medical care as appropriate.

Patients with a serum cholesterol level of 200 mg/dL or greater should have the measurement repeated in one to eight weeks. If the level is within 30 mg/dL of the first result, the average of the two values can be used to guide subsequent decisions; otherwise, a third test should be obtained within another one to eight weeks, and the average of the three values used. Getting more than one cholesterol measurement at the outset of treatment is extremely important to assess the patient's serum cholesterol status accurately, because cholesterol levels can fluctuate considerably from day to day in a given individual. (The standard deviation of repeated measurements in an individual over time has been reported as 18 mg/dL for total cholesterol[4] and 15 mg/dL for LDL-cholesterol.[13])

Most patients with *borderline-high blood cholesterol* levels (200 to 239 mg/dL) confirmed by two or more readings are given dietary education designed to lower their serum cholesterol level and are followed up annually. However, those individuals in the 200-239 mg/dL range who have definite CHD or two other nonlipid CHD risk factors (as defined in Table 4) should have lipoprotein analysis and their LDL-cholesterol level determined.

All patients with *high blood cholesterol* levels (240 mg/dL or greater), as well as those with levels from 200 to 239 mg/dL who have definite CHD or two other

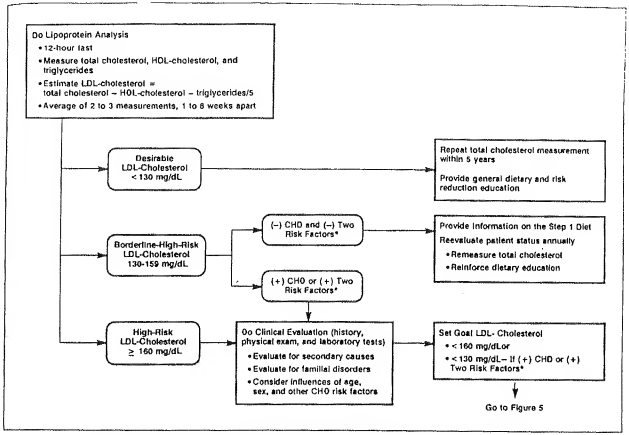

Fig 4.—Classification based on low density lipoprotein (LDL)–cholesterol. Asterisk indicates one of which can be male sex (Table 4); CHD, coronary heart disease; HDL, high density lipoprotein.

CHD risk factors (Table 4), should be tested for the serum level of LDL-cholesterol.

Subsequent Classification Based on LDL-Cholesterol Level.—The action scheme based on LDL-cholesterol level is shown in Fig 4. Two measurements of LDL-cholesterol after an overnight fast are made one to eight weeks apart, and the average is used for clinical decisions unless the two values differ by more than 30 mg/dL (in which case a third test is carried out, and the average of all three is used). The repeated testing of LDL-cholesterol is important for the same reasons given earlier for total cholesterol—the variability of the level from day to day, and the importance of establishing an accurate baseline on which to design the best treatment program. It is possible, however, to save time and effort by making the first LDL-cholesterol measurement on the same specimen that is used for the second test of total cholesterol; this is an especially attractive option for patients with very high levels of total cholesterol (above 260 mg/dL) on the first test.

The LDL-cholesterol levels are classified on the basis of average values as *desirable* (below 130 mg/dL), *borderline-high-risk* (130 to 159 mg/dL), or *high-risk* (160 mg/dL or greater). Patients with desirable LDL-cholesterol fall into the same class as those with desirable total cholesterol levels (<200 mg/dL), and are given general educational materials and tested again within five years. Those with borderline-high-risk LDL-cholesterol (130 to 159 mg/dL) are given information about and advised to follow a fat-modified diet; they are reevaluated annually unless they have definite CHD or two other risk factors (one of which can be male sex [Table 4]). Such patients (with borderline-high-risk LDL-cholesterol who do have CHD or two other risk factors), together with all patients in the high-risk LDL-cholesterol group (≥160 mg/dL), are clinically evaluated as described below, and then enter a cholesterol-lowering treatment program.

Methods of Detection.—Serum *total cholesterol* levels can be measured at any time of day in the nonfasting state, since total cholesterol concentrations do not change appreciably after a fat-containing meal. Patients should be following their ordinary eating habits and be in their usual state of health. Patients who are acutely ill, are losing weight, are pregnant, or have had a myocardial infarction within the past three months should be rescheduled; the cholesterol levels obtained in such patients may not be representative of their usual levels. To prevent an effect of posture or stasis on the cholesterol determination, venipuncture should be carried out on patients who have been in the sitting position for at least five minutes, and the tourniquet should be used for as brief a period as possible. The blood may be collected either as serum (no anticoagulant) or as plasma (in EDTA). If blood is obtained without anticoagulant, it should be allowed to clot for 30 minutes at room temperature, and the clot should be detached from the wall of the tube prior to centrifuging. Rapid capillary blood (fingerstick) methodology for cholesterol measurement is currently under development and evaluation. Should this methodology prove reliable, it could be suitable

for initial cholesterol determination.

Low density lipoprotein–cholesterol determinations can also be carried out on either serum or plasma, provided that, as with total cholesterol measurements, plasma values are multiplied by 1.03 to correct them to the serum cutpoints specified in this report. However, because the LDL-cholesterol value is estimated from measurements of other lipids, including triglyceride, blood samples should be collected from patients who have fasted for at least 12 hours (except for water or black coffee).

The LDL-cholesterol level is estimated from measurements of the levels of total cholesterol, total triglycerides, and HDL-cholesterol. If the triglyceride value is below 400 mg/dL, then this value can be divided by five to estimate the VLDL-cholesterol level. Since total cholesterol is the sum of LDL-cholesterol, HDL-cholesterol, and VLDL-cholesterol, LDL-cholesterol can be calculated as follows (all quantities are in milligrams per deciliter): LDL-Cholesterol = Total Cholesterol − HDL-Cholesterol − (Triglyceride/5).[16] (A recent report suggests that, in this formula, dividing the triglyceride value by 6, rather than 5, may provide a more accurate estimation of the LDL-cholesterol level.[18] Further studies may validate the use of triglyceride/6 as the preferred way of estimating LDL-cholesterol.) If the triglyceride value is above 400 mg/dL, LDL-cholesterol estimation by the above formula becomes less accurate. For such patients, ultracentrifugation in a specialized laboratory can be used to give a more accurate LDL-cholesterol level; it may be appropriate to refer such patients to a lipid specialist.

The choice of laboratory is an important issue because there is considerable variability in the accuracy with which laboratories measure cholesterol. This measurement variability is another reason for recommending that more than one cholesterol measurement be obtained and average values be used at key decision points in this report. All recommendations about cholesterol levels in this report presuppose accurate and reliable measurements. The physician should seek a laboratory that participates in a suitable standardization program. The issue of laboratory methods and their standardization is being addressed by the Laboratory Standardization Panel of the National Cholesterol Education Program.

Clinical Evaluation.—All patients with an LDL-cholesterol level ≥160 mg/dL, and those with a level of 130 to 159 mg/dL and high risk status, as defined in Table 4, should be evaluated clinically. They should then be assigned a goal LDL-cholesterol level and enter the program for cholesterol-lowering treatment.

The clinical evaluation, which includes a history, physical examination, and basic laboratory tests, has three aims. The first is to determine whether the high LDL-cholesterol level is caused by another disease or by a drug. The second is to determine whether a genetic disorder may underlie the elevated LDL-cholesterol. The third aim is to ensure that the patient is fully characterized with regard to age, sex, and the presence or absence of definite CHD and of other CHD risk factors, in order to use this information in decisions about treatment directed at LDL-cholesterol.

Secondary High Blood Cholesterol.—The clinical evaluation for secondary (and possibly reversible) forms of high-risk LDL-cholesterol includes consideration of, and, where appropriate, ruling out, the following conditions: hypothyroidism; nephrotic syndrome; diabetes mellitus; obstructive liver disease; and drugs that may raise LDL-cholesterol levels, particularly progestins and anabolic steroids. High blood cholesterol secondary to other diseases or drugs can be detected by clinical evaluation and, when indicated, by the following laboratory tests: urinalysis, complete blood cell count, and serum thyroid-stimulating hormone (TSH), glucose, alkaline phosphatase, and albumin. When one of the causes of secondary high cholesterol is present, the usual approach is to treat the disease or discontinue the drug (if possible) and then to reevaluate the LDL-cholesterol level.

Familial Disorders.—In most cases, high blood cholesterol is not secondary to some other condition, and the patient has a primary form of LDL-cholesterol elevation. This can be either genetic (familial) or sporadic (often diet induced), and the next step is to consider which of these possibilities is more likely. Diagnosing genetic disorders helps clarify the etiology and management of LDL-cholesterol elevations in affected patients, and emphasizes the desirability of measuring cholesterol in first-degree relatives (parents, siblings, children) in order to identify those who may need cholesterol-lowering treatment.

The genetic hyperlipidemias are described in Appendix II; two important ones are summarized here. One of these is familial hypercholesterolemia (FH), an autosomal dominant disorder of the LDL receptor. Heterozygotes with this disorder have a population frequency of about one in 500 and often have serum cholesterol levels greater than 300 mg/dL, tendon xanthomas, and premature CHD. Another important genetic cause of high-risk LDL-cholesterol levels is familial combined hyperlipidemia (FCHL). Affected family members may have high serum levels of LDL-cholesterol, or of triglyceride, or both. Such patients generally do not have tendon xanthomas, but premature CHD is common. The prevalence of these two familial disorders among survivors of myocardial infarction under 60 years of age is 5% for FH and 15% for FCHL.[20]

Other Lipid Risk Factors.—The level of plasma HDL-cholesterol is inversely related to CHD rates in most epidemiologic studies even after adjustment for the influence of other risk factors (see Appendix II). Although there is no direct experimental evidence that raising HDL-cholesterol levels reduces the risk of CHD, the life-style interventions that raise the level of this lipoprotein—quitting smoking, reducing obesity, and exercising—are good advice for other reasons and should be recommended to all patients regardless of their HDL-cholesterol levels. One other life-style approach to increasing the level of HDL-cholesterol—increasing the intake of alcohol—is not recommended because of the possibility of encouraging excessive intake. The issue of low HDL-cholesterol and its management is discussed further in Appendix II.

Reliance on a ratio of either total or LDL-cholesterol to HDL-cholesterol as a key factor in decisions regarding treatment is not a practice recommended in this report. Blood pressure and smoking are not combined into a single number because the clinician needs to know both facts separately in order to recommend an intervention. Similarly, HDL-cholesterol and LDL-cholesterol are independent risk factors with different determinants, and combining them into a single number conceals information that may be useful to the clinician. The HDL-cholesterol level does, however, contribute to decisions about treatment for LDL-cholesterol, because a low level increases the CHD risk of the patient (Table 4).

The level of plasma triglyceride is also a risk factor for CHD in most epidemiologic studies. In general, however, it is not an independent risk factor, ie, the association usually disappears when statistically adjusted for plasma total cholesterol and HDL-cholesterol levels. In the Framingham Study, however, the plasma triglyceride level was found to be an independent predictor of CHD risk in

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women.[21] The recommended approach to the problem of hypertriglyceridemia is described in the report of the National Institutes of Health Consensus Development Conference on Treatment of Hypertriglyceridemia,[22] and is summarized in Appendix II. In the absence of pathophysiologic or animal evidence that triglyceride is atherogenic or that lowering the plasma level lowers the risk of CHD, intervention specifically directed at this lipid (except in the rare patient with a very high level that may cause pancreatitis) is not generally recommended at this time. On the other hand, many individuals with elevated triglyceride levels have associated low levels of HDL-cholesterol and/or high levels of LDL-cholesterol, which do influence decisions about intervention to reduce the risk of CHD in ways described in this report. Moreover, hypertriglyceridemia alone may be a marker for familial combined hyperlipidemia, which warrants therapy to prevent CHD.

Other Major (Nonlipid) Risk Factors.—Information on whether CHD or its other risk factors are present is used to assess whether the patient has reasons unrelated to LDL-cholesterol for being at high risk of a CHD event or death. The search is important because modifiable risk factors such as hypertension and cigarette smoking are themselves important targets for intervention. In addition, the presence of any risk factor, whether modifiable or not, influences clinical decisions about LDL-cholesterol because the increased absolute level of risk may increase the potential benefit from lowering the level of LDL-cholesterol (Table 3).

This principle can be used in a general way by the clinician, and also as a specific rule in the decision schemes set out in Figs 3 and 4. In Fig 4 the presence of high risk status due to factors other than LDL-cholesterol establishes a lower cutpoint for triggering intervention and a lower therapeutic goal for LDL-cholesterol. The definitions of high-risk status are given in Table 4. Because the presence of CHD is by far the strongest factor that influences the risk of recurrent CHD events or death, it is particularly important in clinical decisions for treating LDL-cholesterol. Thus, this report emphasizes the importance of both primary and secondary prevention.

Age, Race, Sex, and Age.—The percentage of adults with high blood cholesterol by age, race, and sex is given in Table 5. The prevalence rises with age to plateau at about 60 years of age, and does not vary appreciably by race or sex except for the higher prevalence in older women. (This high prevalence in older women is due to the fact that they have high levels of both LDL- and HDL-cholesterol.) Additional information on the distributions of total and LDL-cholesterol levels in the population is given in Appendix I. This section addresses the CHD risk in different groups, with the implications for managing LDL-cholesterol.

Race.—Race is not included in Table 4 because available evidence suggests that the clinical management of LDL-cholesterol should not differ according to race in the United States. (This report is not specifically directed at populations in other countries, but the guidelines would probably apply reasonably well to any country where CHD is endemic at similar levels to those in the United States.)

Sex.—Sex, on the other hand, should be considered as a risk factor, as described in Table 4, when determining the risk status of an individual patient. In women as in men, CHD is the major cause of death, and cholesterol levels are predictive of CHD. However, the rates of CHD are three to four times higher in men than in women in the middle decades of life and roughly two times higher in the elderly.[14,15] Hence, the absolute magnitude of the potential benefit from lowering blood cholesterol in general, and the benefit/risk ratio of drug therapy in particular, is greater for men than for women. Thus, male sex is considered a risk factor in decisions about the cutpoints and goals of cholesterol-lowering treatment.

Table 5.—US Prevalence of High Blood Cholesterol* by Age, Race, and Sex (Percent of Each Population)[23]

	Men		Women	
Age, y	White	Black	White	Black
20-74	25.0	23.9	29.2	23.7
20-24	6.1	2.9	6.5	7.0
25-34	15.0	19.3	12.4	8.7
35-44	27.9	24.5	21.1	16.9
45-54	36.5	40.3	40.6	40.7
55-64	37.3	35.3	53.7	46.5
65-74	32.4	27.2	52.1	48.4

*Serum concentration of cholesterol ≥240 mg/dL.

AGE.—Age is a complicated factor to consider. Beginning at 20 years of age, the mean total and LDL-cholesterol levels increase by about 40 mg/dL during the next two to three decades; in the elderly, the levels decline slightly (see Appendix I for age-specific data). Two major LDL-cholesterol cutpoints are recommended in this report: 160 mg/dL identifies the group with high-risk LDL-cholesterol, and (as discussed later in the section on drug treatment) 190 mg/dL identifies the group with "very-high-risk" LDL-cholesterol for whom consideration of drug therapy is warranted even in the absence of other risk factors. These cutpoints approximate the 75th and 90th percentiles for 35- to 60-year-old patients. Using these same cutpoints in younger patients will have the effect of designating a smaller proportion of the younger population as being in the high-risk categories.

The strategy recommended by the Cholesterol Consensus Conference for making clinical decisions about patients 20 to 39 years of age is to use cutpoints that correspond to the age-specific 75th and 90th percentile values (Appendix I). Using the Consensus Conference recommendations concerning the 75th percentile values, adults 20 to 29 years of age would be considered (in the terminology of the present report) to have high blood cholesterol for levels exceeding 200 mg/dL; those 30 to 39 years of age would be in this category if total cholesterol exceeded 220 mg/dL. Giving dietary treatment to the top 25% of the young adult population is probably desirable in order to prevent the development of atherosclerosis at an earlier stage in the disease. Recommending drug treatment to as large a group as the top 10% of young adults, however, is premature until additional evidence becomes available on the safety of using lipid-lowering drugs for many decades. There is, moreover, the important fact that age is a very strong risk factor, and therefore the absolute magnitude of the benefit (and the benefit/risk ratio) increases with age for the reasons given earlier.

Patients 60 years of age and above are another issue. There is little direct clinical trial evidence on whether elderly patients will benefit from intervention, and the strength of the association between LDL-cholesterol and CHD diminishes with age. However, LDL-cholesterol does continue to have some association with CHD, and the clinical trial evidence for the effectiveness of intervention after myocardial infarction suggests that lowering LDL-cholesterol is beneficial even in patients who already have

Table 6.—Dietary Therapy of High Blood Cholesterol Level

Nutrient	Recommended Intake	
	Step-One Diet	Step-Two Diet
Total fat	Less than 30% of total calories	Less than 30% of total calories
Saturated fatty acids	Less than 10% of total calories	Less than 7% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories	Up to 10% of total calories
Monounsaturated fatty acids	10% to 15% of total calories	10% to 15% of total calories
Carbohydrates	50% to 60% of total calories	50% to 60% of total calories
Protein	10% to 20% of total calories	10% to 20% of total calories
Cholesterol	Less than 300 mg/d	Less than 200 mg/d
Total calories	To achieve and maintain desirable weight	To achieve and maintain desirable weight

advanced disease. Moreover, the fact that age is associated with a high risk of CHD in the later decades of life means that the absolute magnitude of the potential benefits of intervention remains substantial in the elderly.[25]

Summarizing the issue of sex and age, the recommendations and cutpoints in this report are meant to apply to all adults 20 years of age and above. There is room, however, for modifications based on the judgment of the physician and the preferences of the patient when dealing with individual patients, particularly young adults, the elderly, and women.

DIETARY TREATMENT

Cutpoints and Goals for Dietary Therapy

Patients with high-risk LDL-cholesterol levels (≥160 mg/dL), and those with borderline-high-risk LDL-cholesterol (130 to 159 mg/dL) who also have definite CHD or two other risk factors (Table 4), should enter a program of dietary therapy instituted by the physician. The *minimal* goals of therapy are as follows: (1) to lower LDL-cholesterol to below 160 mg/dL if the patient has neither definite CHD nor two other CHD risk factors (Table 4); or (2) to lower LDL-cholesterol to below 130 mg/dL if definite CHD or two other CHD risk factors (Table 4) are present. Ideally, dietary means should be used to attain even lower levels of LDL-cholesterol, if possible, to achieve a further reduction in CHD risk.

Although the goal of therapy is to lower the LDL-cholesterol concentration, measurement of serum total cholesterol can be used to monitor the response to diet. The principle is that LDL-cholesterol should be used for the definitive classification of patients and for decision making, but total cholesterol can be substituted for monitoring. For simplicity, a serum total cholesterol of 240 mg/dL corresponds roughly to an LDL-cholesterol of 160 mg/dL, while a total cholesterol of 200 mg/dL corresponds roughly to an LDL-cholesterol of 130 mg/dL. Thus, as a guide for monitoring, the minimal goals of therapy are: (1) to lower total cholesterol to below 240 mg/dL, if the patient has neither definite CHD nor two other CHD risk factors, or (2) to lower total cholesterol to below 200 mg/dL, if definite CHD or two other risk factors are present. It should be emphasized again that even lower levels of total cholesterol are desirable. The use of total cholesterol as a surrogate for LDL-cholesterol applies to patients with average levels of HDL-cholesterol without high total triglyceride levels. If the patient is found to have an abnormally high or low HDL-cholesterol or hypertriglyceridemia on initial classification, so that total cholesterol is not a good surrogate for LDL-cholesterol, it is appropriate to use LDL-cholesterol even in monitoring. After the cholesterol response to diet has been obtained, LDL-cholesterol should again be measured in order to decide whether or not the goal of therapy has been achieved. In addition, levels of LDL-cholesterol should be employed for making a decision about drug therapy.

Overview and General Approach

Three dietary habits typically contribute significantly to elevated plasma cholesterol. First is a high intake of saturated fatty acids. The average intake is 13% to 15% of total calories, but many Americans consume 15% to 20% of their calories as saturated fatty acids. Second is a relatively high intake of cholesterol. Many patients with high-risk LDL-cholesterol levels exceed the current average intake of about 350 to 450 mg/d. Third is a high caloric intake that exceeds body requirements commonly causing obesity. The aim of dietary therapy is to reverse these excesses while maintaining and promoting good nutrition.

This document is directed at the high-risk patient, and its underlying theme is specific therapy for high blood cholesterol. Modification of the diet is an essential element in this therapy. The initial diet modifications recommended for patients in this report are very similar to the diet modifications recommended by the American Heart Association (Dallas) and other organizations for the public at large, as part of a population-based approach for lowering cholesterol. In the program described in this report, however, diet recommendations are provided to patients, in a medical treatment setting, in an intensive manner. Accordingly, the dietary intervention described here is referred to as "dietary treatment." It should be noted that the diets recommended in this report are consistent with good nutrition, and that their aim is to achieve healthy eating patterns. Physicians should emphasize to patients that the goal is not a temporary "diet," but a permanent change in eating behavior.

Diet modification should occur in two steps, which are outlined and compared in Table 6. These diets are designed to progressively reduce the intake of saturated fatty acids and cholesterol and eliminate excess total calories. The Step-One Diet should be prescribed by the physician and implemented by the physician and his or her immediate staff. This diet calls for an intake of total fat less than 30% of calories, saturated fatty acids less than 10% of calories, and cholesterol less than 300 mg/d. The patient's serum cholesterol level should be measured at four to six weeks and at three months after starting the Step-One Diet.

If the *minimal* goals of therapy are not achieved on this diet by three months, the patient should usually progress to the Step-Two Diet. Adoption of the Step-Two Diet would be facilitated by referral to a registered dietitian. This diet

calls for a further reductic saturated fatty acid intake to less than 7% of calories and cholesterol intake to less than 200 mg/d.

For many high-risk patients, the goals of cholesterol lowering can be achieved by dietary therapy alone. It is important that dietary therapy not be regarded as a failure prematurely. For most patients, dietary therapy should be continued for at least six months before adding drug therapy. Exceptions include patients with very-high LDL-cholesterol levels and other severe dyslipidemias (see Appendix II). If the desired goals of LDL-cholesterol lowering are met by diet modification alone, long-term monitoring is indicated. If reduction of LDL-cholesterol is not satisfactory, lipid-lowering drugs should be considered along with continued dietary intervention. (For detailed information about the effects of diet on serum lipids and lipoproteins and on CHD risk, including key studies and reviews, the reader should consult references 26 through 46.)

Recommended Diets

Step-One and Step-Two Diets—Nutrients and Rationale.—The recommended diets are presented in two steps—the Step-One and Step-Two Diets. The Step-One Diet calls for the reduction of the major and obvious sources of saturated fatty acids and cholesterol in the diet; for many patients this can be achieved without a radical alteration in dietary habits. The Step-Two Diet requires careful attention to the whole diet so as to reduce the intake of saturated fatty acids and cholesterol to a minimal level compatible with an acceptable and nutritious diet. Saturated fatty acids and cholesterol are not essential nutrients, and neither is required in the diet. The body can make these lipids in abundance, and they can be transported from one tissue to another to assure that any local shortage is supplied by lipids produced elsewhere in the body. The real need then is to reduce dietary saturated fatty acids and cholesterol to the levels required to achieve the goals of LDL-cholesterol lowering and still provide a diet that is nutritious and palatable. The fat-modified diets proposed in this report are designed to achieve these aims. The rationale for the recommended characteristics of the Step-One and Step-Two Diets can be described briefly.

A Nutritionally Balanced Diet.—A prerequisite for any therapeutic diet is that it be nutritionally adequate." It must contain sufficient amounts of vitamins, minerals, and macronutrients to meet recommended allowances. The diet should contain a variety of foods. Fruits, vegetables, and legumes (peas and beans) are good sources of vitamin A, vitamin C, folic acid, fiber, and many minerals. Whole-grain and enriched breads, cereals, and other grain products contain B vitamins, protein, fiber, and some iron. Poultry and fish are good sources of protein. Meat products are rich in protein and contain iron in a form that is well absorbed; thus, meat can be included in a diet otherwise designed to lower serum cholesterol, although meat fat needs to be curtailed. The same is true of milk products; the nonfat portion of milk is rich in calcium and contains protein. While egg yolks are rich in cholesterol, egg whites contain protein and no cholesterol. Most nuts contain protein and fat, but their fat is largely unsaturated and thus does not raise the serum cholesterol level. Thus, while a serum-cholesterol-lowering diet requires modification of fat, the diet should be nutritious and palatable and include a variety of foods. The following considers the specific modifications that will be required.

Total Fat.—Total fat intake in both therapeutic diets should not exceed 30% of total calories. The purpose of decreasing total fat intake is twofold—to facilitate reduction of saturated fatty acid intake and to promote weight reduction in overweight patients by substituting foods of lower caloric density. Total fat in the current American diet averages approximately 35% to 40% of calories. Hence, for most high-risk patients, about one-fifth of their total fat now consumed must be eliminated. In the past, one approach to more intensive dietary therapy of high blood cholesterol (beyond the Step-One Diet) has been to reduce intake of total fat to 20% or less of calories, in parallel with progressive reductions in saturated fatty acids and cholesterol. However, very low fat intakes have low satiety value and often are not well accepted. Recent evidence indicates that a marked reduction in dietary fat is not required for satisfactory lowering of plasma LDL, provided that saturated fatty acids are reduced and the remaining fat is mainly unsaturated. In other words, a decrease in total fat to below 30% of calories may not be needed for the sole purpose of lowering the plasma cholesterol level. Nevertheless, a reduction in total fat to near 20% of calories will facilitate weight reduction and a decrease in saturated fatty acid intake for some patients. For these reasons, a further reduction of fat intake is not required in the Step-Two Diet, but neither is it excluded.

Saturated Fatty Acids.—In the Step-One Diet, saturated fatty acids should be decreased to less than 10% of calories. For most patients, saturated fatty acid intake will have to be reduced by about one-third to meet the requirements of the Step-One Diet, and another third for the Step-Two Diet. Several dietary fats are rich in saturated fatty acids. Animal fats that are high in saturated fatty acids include butter fat—contained in butter itself, whole milk, cream, ice cream, and cheese—beef fat, and pork fat. In addition, three plant oils—palm oil, palm kernel oil, and coconut oil—are especially rich in saturated fatty acids.

Polyunsaturated Fatty Acids.—When dietary saturated fatty acids are decreased, they can be replaced in part by polyunsaturated fatty acids. The polyunsaturates can be increased to 10% of calories, but they should not exceed this value. The current American diet contains about 7% of calories as polyunsaturated fatty acids, which should be a minimum value for the therapeutic diets. There are two major categories of polyunsaturated fatty acids, commonly referred to as omega-6 and omega-3. The major omega-6 fatty acid is linoleic acid, which has 18 carbon atoms and two double bonds. Substitution of linoleic acid for dietary saturated fatty acids results in a fall in the plasma cholesterol level. Although very high intakes of linoleic acid were once advocated for cholesterol lowering, lack of information about the consequences of long-term ingestion of large amounts of linoleic acid has led most investigators to recommend a ceiling of 10% of total calories. Several vegetable oils are rich in linoleic acid, including safflower oil, sunflower seed oil, soybean oil, and corn oil. Although polyunsaturated oils are high in linoleic acid and low in saturated fatty acids, they also are high in total calories (as are all fats and oils); consequently they can promote weight gain if consumed in large amounts.

The major sources of omega-3 fatty acids are the fish oils. Most omega-3 fatty acids in fish oil have very elongated carbon chains and are highly polyunsaturated. The major acids in this class are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The omega-3 fatty acids have been found to lower triglyceride levels when given in high doses, but they are not necessarily the desired therapy for hypertriglyceridemia (Appendix II). There is little evidence that omega-3 fatty acids are useful for reducing LDL-cholesterol levels. Although it has been postulated

by. some that they will reduce risk for CHD, this has not been established. Furthermore, it is not known whether long-term ingestion of these fatty acids will lead to undesirable side effects. The use of fish-oil capsules as a supplement in a therapeutic diet for high-risk cholesterol levels is not recommended here.

Consumption of omega-3 fatty acids should be differentiated from that of fish. Some fish are rich in omega-3 acids while others are not. Epidemiologic data suggest that frequent consumption of fish of any type, seemingly independent of omega-3 fatty acids, is associated with reduced CHD risk. Whether this is true or not, fish can serve as a useful substitute for meats that are richer in saturated fatty acids.

Monounsaturated Fatty Acids.—In both therapeutic diets, monounsaturated fatty acids, mainly oleic acid, should comprise 10% to 15% of total calories. Oleic acid is the major fatty acid found in olive oil, rapeseed (canola oil), and high-oleic forms of sunflower seed oil and safflower oil. For many years, oleic acid was considered to be "neutral" in its effect on plasma cholesterol, neither raising nor lowering the cholesterol level. However, recent evidence indicates that oleic acid may cause as much of a decrease in LDL-cholesterol levels as linoleic acid when either is substituted for saturated fatty acids in the diet. The current American diet contains 14% to 16% of calories as monounsaturated fatty acid. Much of it is consumed with animal fats, which are rich in saturated fatty acids. When animal fats are curtailed, a larger portion of monounsaturated fatty acids can come from vegetable oils.

Dietary Cholesterol.—Dietary cholesterol causes marked hypercholesterolemia and atherosclerosis in many laboratory animals, including nonhuman primates. Although high intakes of cholesterol in humans rarely cause striking rises in the plasma cholesterol level, controlled metabolic studies show that dietary cholesterol usually raises the plasma cholesterol level. The degree of rise varies from person to person. Overall, excess dietary cholesterol appears to contribute to the high LDL-cholesterol levels seen in high-risk patients and thus may add to CHD risk. Furthermore, concern about dietary cholesterol extends beyond its effects in raising the LDL-cholesterol level. Newly absorbed cholesterol enters the circulation with chylomicrons, which are degraded to cholesterol-rich chylomicron remnants; the latter may be atherogenic. Dietary cholesterol is not required for normal body function.

For practical purposes, a cholesterol intake of less than 300 mg/d is reasonable as part of the first step in dietary management of high-risk LDL-cholesterol. However, further restriction, as recommended in the Step-Two Diet, is justified for patients who do not achieve the goals of therapy on the Step-One Diet, despite adherence. Cholesterol in the diet comes from animal products. Particularly rich sources are egg yolk and organ meats (liver, sweetbreads, and brain). Some shellfish (eg, shrimp) also are moderately high in cholesterol, but not to the extent of egg yolk or organ meats. The flesh of all animals (beef, pork, lamb, chicken, fish) contains cholesterol; it is present in both muscle and fat, and both have approximately the same concentrations on a wet-weight basis. Dairy products containing butter fat also contribute cholesterol to the diet.

Protein.—The recommended intake of protein in both therapeutic diets is between 10% and 20% of calories. In laboratory animals, certain plant proteins have a cholesterol-lowering action relative to animal proteins. The same effect has not been established in humans. Thus, the type of protein in the therapeutic diets is not specified.

Carbohydrate. Both recommended diets specify an intake of carbohydrates of 50% to 60% of calories. When dietary fat is reduced, it should be replaced by carbohydrate. Dietary carbohydrates include simple sugars (monosaccharides and disaccharides), complex digestible carbohydrates (starches), and complex indigestible carbohydrates (fiber). Complex carbohydrate should comprise more than half of digestible carbohydrates; this will help ensure ingestion of desirable quantities of vegetable products that contain vitamins, minerals, and fiber. In most people, when digestible carbohydrates are substituted for cholesterol-raising saturated fatty acids, the LDL-cholesterol level will fall to about the same extent as when oleic acid and linoleic acid are substituted in this manner. Very-high-carbohydrate diets can raise plasma triglycerides, but when fat intakes are in the vicinity of 30% of calories, this triglyceride response is minimal.

Total Calories.—Obesity is not only associated with elevated serum LDL-cholesterol levels, but is an independent risk factor for CHD. An important recommendation, therefore, is to reduce caloric intake to achieve weight reduction in overweight patients. Weight reduction will lower the LDL-cholesterol level in many people, as well as reduce plasma triglycerides and raise HDL-cholesterol levels. Some patients with high-risk LDL-cholesterol levels are extremely sensitive to caloric intake, and weight reduction and establishment of desirable body weight will completely correct their elevated LDL-cholesterol concentrations. The importance of caloric restriction in overweight, high-risk individuals cannot be overemphasized.

Weight reduction can be facilitated by exercise. Experience has shown that regular exercise will curb the appetite as well as burn off excess calories. It also will lower serum triglycerides and raise HDL-cholesterol levels, and, in some individuals, may lower the LDL-cholesterol level.

Fiber.—The indigestible carbohydrates and related polymers come under the category of dietary fiber. One type of fiber is insoluble, an example of which is the cellulose found in wheat bran. Insoluble fiber adds bulk to the stools and contributes to normal colon function. Some authorities believe that a relatively high intake of dietary fiber may help prevent diverticulosis and colon cancer, although this remains to be proven. Excessive intakes of insoluble fibers can be associated with gastrointestinal side effects and even interfere with absorption of vital nutrients such as calcium. Dietary fibers such as cellulose appear to have very little or no effect on blood cholesterol levels.

Another type of fiber is soluble in the intestine but not absorbed. This category includes pectins, certain gums, and psyllium. One of the gums is β-glucan, which is present in oat products and beans. High intake (eg, 15 to 25 g/d) of soluble fiber has been reported to lower the plasma cholesterol level by 5% to 15%. This high intake can produce gastrointestinal side effects, but prolonged usage frequently is associated with improved tolerance.

Alcohol.—The average intake of alcohol among Americans is approximately 5% of total calories, but this value varies widely among individuals. Although alcohol is not harmful when taken in moderation, a high consumption is known to have many adverse effects on health. Alcohol affects lipoprotein metabolism in several ways. It does not affect LDL-cholesterol concentrations, but it does increase triglyceride concentrations and HDL-cholesterol levels in many individuals. The mechanism for the rise in HDL-cholesterol is not known, nor is it known whether the higher level so produced imparts any protection against CHD. For patients who can consume moderate amounts of alcohol responsibly, its use can be allowed in the context of

Table 7.—Recommended Diet Modifications to Lower Blood Cholesterol Levels

	The Step-One Diet	
	Choose	Decrease
Fish, chicken, turkey, and lean meats	Fish, poultry without skin, lean cuts of beef, lamb, pork or veal, shellfish	Fatty cuts of beef, lamb, pork; spare ribs, organ meats, regular cold cuts, sausage, hot dogs, bacon, sardines, roe
Skim and low-fat milk, cheese, yogurt, and dairy substitutes	Skim or 1% fat milk (liquid, powdered, evaporated), buttermilk	Whole milk (4% fat); regular, evaporated, condensed; cream, half and half, 2% milk, imitation milk products, most nondairy creamers, whipped toppings
	Nonfat (0% fat) or low-fat yogurt	Whole-milk yogurt
	Low-fat cottage cheese (1% or 2% fat)	Whole-milk cottage cheese (4% fat)
	Low-fat cheeses, farmer or pot cheeses (all of these should be labeled no more than 2 to 6 g of fat per ounce)	All natural cheeses (eg, blue, roquefort, camembert, cheddar, Swiss), low-fat or "light" cream cheese, low-fat or "light" sour cream, cream cheeses, sour cream
	Sherbet, sorbet	Ice cream
Eggs	Egg whites (2 whites equal 1 whole egg in recipes), cholesterol-free egg substitutes	Egg yolks
Fruits and vegetables	Fresh, frozen, canned, or dried fruits and vegetables	Vegetables prepared in butter, cream, or other sauces
Breads and cereals	Homemade baked goods using unsaturated oils sparingly, angel food cake, low-fat crackers, low-fat cookies	Commercial baked goods: pies, cakes, doughnuts, croissants, pastries, muffins, biscuits, high-fat crackers, high-fat cookies
	Rice, pasta	Egg noodles
	Whole-grain breads and cereals (oatmeal, whole wheat, rye, bran, multigrain, etc)	Breads in which eggs are a major ingredient
Fats and oils	Baking cocoa	Chocolate
	Unsaturated vegetable oils: corn, olive, rapeseed (canola oil), safflower, sesame, soybean, sunflower	Butter, coconut oil, palm oil, palm kernel oil, lard, bacon fat
	Margarine or shortenings made from one of the unsaturated oils listed above, diet margarine	
	Mayonnaise, salad dressings made with unsaturated oils listed above, low-fat dressings	Dressings made with egg yolk
	Seeds and nuts	Coconut

the above reservation. However, this report does not specifically recommend use of alcohol in the prevention of CHD.

Expected Responses to Dietary Therapy.—The degree of reduction of LDL-cholesterol levels that can be achieved by dietary therapy depends on the dietary habits of the patient before starting the diet and on the inherent responsiveness of the patient. In general, patients with high cholesterol levels show a greater absolute reduction in total and LDL-cholesterol concentrations than do individuals with relatively low cholesterol levels. Metabolic ward studies suggest that switching from the typical American diet to the Step-One Diet could reduce cholesterol levels on average by 30 to 40 mg/dL. Advancing to the Step-Two Diet can be expected to cause a further decline of approximately 15 mg/dL in cholesterol levels. Some individuals may demonstrate even greater reductions on the two diets, and others will have lesser responses. Most of the decrease in total blood cholesterol occurs in the LDL fraction.

Practical Approach to Dietary Therapy

Outline of Approach.—Once a patient is deemed at high risk, dietary therapy should begin in the physician's office. Diet is the cornerstone of treatment of high-risk cholesterol levels. The view that diet modification is impractical or doomed to failure for most patients is not justified. Many individuals have successfully modified their diets and have obtained a substantial reduction in cholesterol levels. Much of the problem of high cholesterol levels among Americans is due to dietary excesses, and diet modification is the rational approach to this problem for most people.

Role of the Physician.—The success of dietary therapy will depend to a large extent on the physician's attitudes, knowledge, and skills in motivating the patient and in organizing a team approach to dietary therapy. The physician can have a major impact on the patient's attitude toward diet modification. A positive attitude on the part of the physician is absolutely vital. The physician should describe to the patient his/her category of high blood cholesterol and should give an overview of the therapeutic plan. The role of diet, and possibly drugs, should be discussed. The physician will need to review the patient's dietary history. The patient should be questioned about current dietary habits with special attention to intake of foods rich in saturated fatty acids and cholesterol (eg, dairy fats—milk, butter, cheese, ice cream—frequency and choices of meat products, bakery goods, eggs, and organ meats). The need to modify eating behavior to achieve the

goals of therapy should be indicated, and the plan for carrying out dietary treatment, as it involves other members of the team, can be described. Finally, the physician has a vital role to play in the monitoring of response, in reinforcement of the diet message, and in leadership of the therapeutic team. For assessing adherence to the diet, the physician can review the contents of Table 7 with the patient at follow-up visits.

Role of the Physician's Staff.—Another key component of the therapeutic team is the physician's staff. This may include registered nurses, registered physician's assistants, nurse clinicians, and other types of assistants. These individuals should receive appropriate training for their roles in patient management, which will include aiding in further dietary assessment and in dietary education and counseling. Nurses and other assistants can play key roles in patient education (eg, rationale for dietary change, selection of appropriate foods), in promoting behavioral changes, and in monitoring dietary changes. Various educational materials produced by the National Cholesterol Education Program and the American Heart Association can be used to assist in dietary education for patients. Referral to a registered dietitian can facilitate dietary instruction and monitoring of adherence, but if the physician's staff is appropriately trained, it can perform these functions for many patients.

Role of Registered Dietitians.—Registered dietitians (RDs) are educated in the science of nutrition and are professionally trained in dietary intervention. They must meet uniform standards for registration. The term "nutritionist" is used in a variety of ways. Some nutritionists are registered dietitians, but others may not be registered and may not have the clinical training in dietary counseling of a registered dietitian. Although such nutritionists may play a role in dietary education, referral to a registered dietitian is particularly valuable for more intensive dietary therapy, such as the Step-Two Diet, and evaluation of nutritional adequacy. Patients who have had difficulty in adhering or responding to the Step-One Diet also have much to gain from counseling by a registered dietitian. Patients who are not initially successful in the Step-One Diet may be referred to a dietitian for another Step-One Diet trial period before progressing to the Step-Two Diet. For some patients, based on the physician's judgment, referral to a registered dietitian may be appropriate from the outset of dietary therapy.

Dietitians can be identified through a local hospital as well as through state and district affiliates of the American Dietetic Association (208 S LaSalle St, Chicago, IL 60604). The American Dietetic Association maintains a roster of dietitians and responds to requests in writing for assistance in locating a registered dietitian in a given area. Dietitians with particular expertise in cholesterol management are available in most large medical centers where they are often part of a multidisciplinary lipid clinic team or cardiac rehabilitation team. The local affiliate of the American Heart Association may have a listing of dietitians who have particular interest and expertise in modifying the diet for purposes of cardiovascular risk reduction.

Schedule of Dietary Therapy.—Adherence to the prescribed diet is facilitated by monitoring the patient's response. The Step-One Diet should be employed for three months, and if the desired response is not obtained in spite of good diet adherence, the patient can progress to the Step-Two Diet for another three months. During this period, serum cholesterol levels should be monitored at regular intervals (described below). For most patients, dietary therapy to lower serum total and LDL-cholesterol should be employed for at least six months before considering drugs. Exceptions to this approach are patients with severe elevations of serum cholesterol (Appendix II) and patients with definite CHD.

Recommended Dietary Patterns.—Most patients should be able to adopt and adhere to the Step-One Diet. Table 7 outlines ways to achieve the goals of dietary therapy, and a copy may be given to the patient along with additional educational materials. It should be emphasized to the patient that the recommended diet can be both tasty and nutritious, and that many choices of high-quality and acceptable foods are available in stores and restaurants.

A few general dietary changes underlie implementation of the Step-One Diet. To decrease intake of total fat, saturated fatty acids, and cholesterol, attention should be given to reducing foods containing butter fat—butter itself, cheese, ice cream, cream, whole (4%) milk, and even 2% milk. Only lean cuts of meat should be selected, visible fat should be trimmed away, and fat should be allowed to drain from meat after cooking. The skin of chicken should be removed, and fish should be substituted frequently for meat. Consumption of egg yolks and organ meats (liver, brain, sweetbreads) should be reduced. Shrimp, lobster, and other shellfish contain varying amounts of cholesterol, but are low in fat, and thus may be eaten occasionally. The vegetable oils rich in saturated fatty acids—coconut oil, palm kernel oil, and palm oil—are used in some commercial foods and food products; products that list these oils as ingredients on the label should generally be avoided.

Specific Food Subgroups.—Special attention should be given to certain common foods in the diet. This subsection provides specific recommendations:

MEATS.—Beef, pork, and lamb.—Use *lean* cuts of beef, pork, and lamb. Lean cuts of beef include extra-lean ground beef, sirloin tip, round steak, rump roast, arm roast or center-cut ham, loin chops, and tenderloin. Trim all fat off the outside of meats before cooking. It is not necessary to severely curtail the intake of red meat. Lean meat is rich in protein and contains a highly absorbable form of iron. Premenopausal women in particular should avoid severe reduction of lean red meat that would increase the risk for iron-deficiency anemia.

Processed meats.—Eat very little high-fat processed meats—bacon, bologna, salami, sausage, and hot dogs. Processed meats contain large quantities of "hidden" fat, and they are not rich in valuable nutrients.

Organ meats.—The organ meats—liver, sweetbreads, kidneys, and brain—are very rich in cholesterol, and they should be limited.

Chicken and turkey.—These are good sources of protein. The fat of poultry should be reduced by removal of skin and underlying fat layers. Chicken and turkey can be substituted for lean red meat in the diet, but they do not contain as much iron. Chicken and poultry should not be fried in fats rich in saturated fatty acids or covered with fat-rich sauces.

Fish.—Fish are a good source of protein. They contain cholesterol, but usually are low in saturated fatty acids. The preparation of fish is important. Like chicken and turkey, they should not be fried in saturated fats or covered with fat-rich sauces.

Shellfish.—Most shellfish contain less fat than meat and poultry. Their cholesterol content is variable (see Table 8). Some shellfish (eg, shrimp) are relatively high in cholesterol, but even these can be eaten occasionally within the recommended guidelines for cholesterol intake.

A reasonable approach to meat consumption is to limit intake of lean meat, chicken, turkey, and fish to six ounces

Table 8.—Cholesterol and Fat Content of Animal Products in Three-Ounce Portions (Cooked)

Source	Cholesterol Content, mg/3 oz	Total Fat Content, g/3 oz
Red meats (lean)		
Beef	77	8.7
Lamb	78	8.8
Pork	79	11.1
Veal	128	4.7
Organ meats		
Liver	270	4.0
Pancreas (sweetbreads)	400	2.8
Kidney	329	2.9
Brains	1746	10.7
Heart	164	4.8
Poultry		
Chicken (without skin)		
Light	72	3.8
Dark	79	8.2
Turkey (without skin)		
Light	59	1.3
Dark	72	6.1
Fish		
Salmon	74	9.3
Tuna, light canned in water	55	0.7
Shellfish		
Abalone	90	0.8
Clams	57	1.7
Crab meat		
Alaskan King	45	1.3
Blue crab	85	1.5
Lobster	61	0.5
Oysters	93	4.2
Scallops	35	0.8
Shrimp	166	0.9

per day. The cholesterol and total fat content per three ounces (the recommended portion size) of various cooked meats are presented in Table 8.

Dairy Products.—Use skim milk or 1% milk instead of 2% or whole milk, which contains approximately 4% fat. Decrease natural and processed cheeses; substitute low-fat (2%) cottage cheese or synthetic cheeses produced from vegetable oils. Choose yogurt of the nonfat or low-fat (1% to 2%) type. Experiment with evaporated skim milk in recipes calling for heavy cream. Substitute low-fat yogurt or low-fat cottage cheese for sour cream in dips and salad dressings. Have at least two servings of very-low-fat dairy products, such as two glasses of skim (or 1%) milk, daily to help maintain calcium intake.

Fats and Oils.—The general rule is to reduce intakes of fats and oils that are high in saturated fatty acids and cholesterol. Butter fat is high in both and should be curtailed as much as possible. Lard and beef fat are other blood cholesterol–raising animal fats. Vegetable fats do not contain cholesterol. However, certain vegetable fats—coconut oil, palm oil, and palm kernel oil—are very high in saturates and should be avoided; these fats are often used in bakery goods, processed foods, popcorn oils, and nondairy creamers. Labels on these foods should be read carefully to detect the presence of saturated vegetable oils.

Unsaturated vegetable oils and fats do not raise blood cholesterol, but they should be limited because they are high in calories. Generally, up to six to eight teaspoons a day is acceptable. Desirable liquid vegetable oils are corn oil, cottonseed oil, olive oil, rapeseed (canola) oil, safflower oil, soybean oil, and sunflower oil. Peanut oil is less desirable, but small amounts are acceptable. Margarine represents partially hydrogenated vegetable oil and is preferable to butter. Vegetable shortenings fall into the same category as margarine. Both contain quantities of *trans* fatty acids; these are not naturally occurring and should not be taken in excess. Mayonnaise and salad dressings often are made from unsaturated fats, but they too should be limited because of their high caloric content.

Eggs.—Eat no more than three egg yolks in a week on the Step-One Diet, and no more than one per week on the Step-Two Diet. Egg yolks often are hidden in cooked and processed foods. Egg whites contain no cholesterol, and they can be eaten often. Experiment with one to two egg whites instead of whole eggs in recipes, or use commercial egg substitutes that do not contain yolk.

Fruits and Vegetables.—It is advisable to feature fruits and vegetables as an important part of each meal. Both are rich in vitamins, fiber, and some minerals, and contribute to achieving the recommended allowances of these nutrients. Certain green and yellow vegetables may reduce the risk for cancer. Fruits (and even vegetables) can be used for snacks and desserts.

Breads, Cereals, Pasta, Rice, Dried Peas, and Beans.—These products are high in carbohydrate and protein and most are low in fat. Therefore, they can be increased in the diet as substitutes for fatty foods. However, they too contain calories and must not be eaten in excess. Cereals can be eaten as snacks as well as for breakfast. Dried peas and beans are good sources of protein. Combine large quantities of pasta, rice, legumes, and vegetables with smaller amounts of lean meat, fish or poultry to derive complete protein sources with less fat and calories.

Nuts.—Nuts tend to be high in fat, but the fat usually is unsaturated. The intake of nuts should thus be limited mainly to avoid excess calories. The same is largely true for peanut butter.

Other Eating Tips.—Snacks.—Most candies should be limited as snacks; they tend to be rich in simple sugars and fats, and their caloric content outweighs their nutritional value. Some good choices in snacks are graham crackers, rye krisp, melba toast, soda crackers, bagels, English muffins, fruit, ready-to-eat cereals, and vegetables; these are preferable to snack crackers, french fries, and chips. Popcorn should be air popped or cooked in small amounts of liquid vegetable oil.

Desserts.—Eat fruits, low-fat fruit yogurt, and fruit ices instead of pastries, cake, and cookies. Also acceptable are sherbet, angel food cake, jello, frozen low-fat yogurt, and, occasionally, ice milk.

Cooking Methods.—Choose those methods that use little or no fat. They include steaming, baking, broiling, grilling, or stir-frying in small amounts of fat. Foods can be cooked in the microwave or in a nonstick pan without added fat. Limit fried foods and avoid frying in saturated fats. Soups and stews should be chilled after cooking, and the congealed fat that forms on top after a few hours in the refrigerator should be skimmed off. When preparing meals avoid use of excess sodium, which can contribute to raising blood pressure in some people.

Eating Away From Home.—Order entrees, potatoes, and vegetables without sauces or butter. When meat exceeds the size of a deck of cards (three to four ounces), the rest can be taken home for another meal. Choose

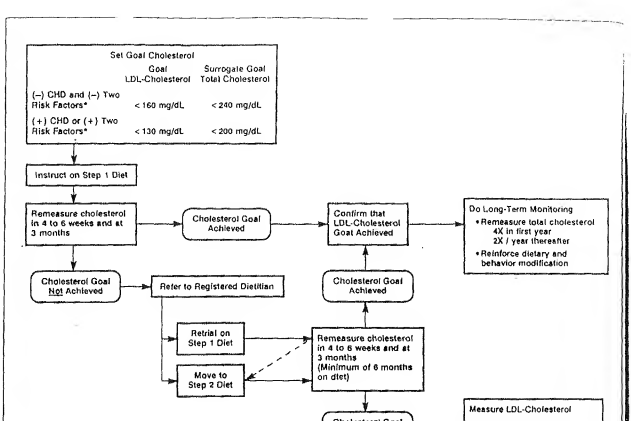

Fig 5.—Dietary treatment. Asterisk indicates one of which can be male sex (Table 4); LDL, low density lipoprotein; CHD, coronary heart disease.

vegetable or fruit salads, and ask for salad dressings to be served on the side; use dressings sparingly. Limit high-fat toppings such as bacon, crumbled eggs, cheese, sunflower seeds, and olives, the latter two because they may be high in fat and salt. Ask for margarine instead of butter, and limit the amount of margarine used on bread and baked potatoes.

The physician who follows patients with high blood cholesterol frequently will be asked about specific food items. It may be helpful for the physician to have available a reference on food composition.[42,43]

Behavioral Modification.—Long-term adherence to the recommended diets can be achieved only through permanent modification of eating behavior. Several factors are required to achieve long-term success in adapting to a new diet. The rationale for diet change can be provided by the physician. Education of the patient in the principles of the fat-modified diet is the responsibility of the physician, the physician's immediate staff (eg, nurses), and, when utilized, a registered dietitian. The effectiveness of this approach will be facilitated by frequent communication among the different members of the team. Followup and monitoring by physicians is a key element in achieving the goals of LDL lowering on a long-term basis. Sometimes, permanent modification of eating behavior will require prolonged interaction with a registered dietitian. A brief summary of the process of dietary instruction and behavior modification as practiced by dietitians is provided in Appendix III. This discussion may guide physicians in their own instructions to the patient.

An important adjunct to long-term change in eating behavior and life-style is a regular exercise program. Especially useful forms of exercise are activities that require movement of the body over distance, such as walking, stair climbing, running, cycling, and swimming. Improvements in cardiovascular fitness result from exercising regularly at moderate intensity for 15 to 30 minutes at least every other day. However, vigorous exercise must be carried out with caution in high-risk persons, and only with the advice of a physician and under the supervision of trained personnel.

Monitoring and Followup

Step-One Diet.—After starting the Step-One Diet, the serum total cholesterol level should be measured at four to six weeks and at three months (Fig 5). This will allow the patient enough time to adopt new eating habits and to respond to the dietary change. At the end of three months, the physician should assess the patient's adherence to the diet plan and response to dietary therapy. The response can be judged on the basis of the change in serum cholesterol level. If the response is satisfactory, ie, if the total cholesterol monitoring goal is met (<240 mg/dL without definite CHD or two other risk factors, <200 mg/dL with definite CHD or two other risk factors [Table 4]), then the LDL-cholesterol level should be mea-

sured in order to confirm that the LDL-cholesterol goal has been met. If the LDL goal is met, the phase of long-term monitoring can begin. If the response is not satisfactory, the patient should generally be referred to a registered dietitian and should progress to the Step-Two Diet or to another trial on the Step-One Diet. If this latter approach is selected, the patient should again be evaluated after four to six weeks and three months, with progression to the Step-Two Diet if the response is still not satisfactory.

Step-Two Diet.—On the Step-Two Diet, serum cholesterol levels should be measured after three to four weeks and three months of therapy. After three months of treatment with the Step-Two Diet, the physician should again assess the patient's adherence and response to the diet. It is important to document the extent of adherence to the therapeutic diet. If the desired goal for serum cholesterol–lowering has been attained, and a measurement of LDL-cholesterol level confirms that the LDL goal has been met, long-term monitoring can begin; if not, consideration should be given to drug therapy.

Diet Success: Long-term Monitoring.—The patient who has achieved the target goals for lowering of LDL-cholesterol by dietary therapy can be declared a diet success. Monitoring of total cholesterol should be carried out on a long-term basis. The fat-modified diet should be maintained indefinitely and the patient should be encouraged to adhere to the recommended eating pattern. Diet education should be continued and reinforced, by a registered dietitian if necessary. The patient should be counseled quarterly for the first year of long-term monitoring and twice yearly thereafter.

Total serum cholesterol should be measured prior to each visit, and the results should be used at the counseling session. For patients who have no lipoprotein abnormalities other than elevated LDL-cholesterol, monitoring at six-month intervals is appropriate. In such patients, the total cholesterol measurement, which can be made with a non-fasting blood sample and is less expensive than lipoprotein analysis, will provide a reasonable index of the LDL-cholesterol level. Many patients who previously have had high cholesterol levels on the typical American diet are "diet sensitive," which explains their originally high level. This means that continuous attention must be given to dietary adherence to avoid a "relapse" to high cholesterol concentrations. If the patient redevelops an elevated cholesterol level, the procedure outlined above for dietary therapy of elevated LDL-cholesterol may have to be reinstituted.

Inadequate Response to Diet.—A patient who fails to achieve the goals for lowering of total cholesterol (or LDL-cholesterol) by dietary therapy should be classified as having an inadequate response to diet. This does not necessarily mean diet failure, because a significant reduction in cholesterol levels may have occurred by diet modification. There are four categories of inadequate response to diet that can be distinguished.

1. Patients who have severe elevations of serum cholesterol often cannot achieve the goals of serum cholesterol lowering by diet, no matter how strict the diet. For these patients (Appendix II), it is not necessary to wait for six months of dietary therapy before adding drugs to the regimen.

2. Some patients with high LDL-cholesterol levels are biologically relatively resistant to LDL lowering by diet modification and will not achieve the cholesterol lowering goal despite good adherence to diet.

3. Others will adhere poorly to diet in spite of an intensive effort by the physician and counselors. After a few months it will be obvious that these patients will not adhere to dietary recommendations. Some physicians have the mistaken belief that most patients fall into this category, but this certainly is not true. A concerted effort by the physician, immediate staff, and registered dietitian should minimize the size of this group of patients.

4. For still other patients, a more prolonged period of dietary therapy may be justified. Up to a year, or even longer, may be required for a patient to learn to modify the diet by changing both the pattern of diet and eating habits. There may be a tendency for some physicians to employ drugs too soon instead of making the effort to change the patient's dietary habits. This tendency must be resisted. Adequate time should be allowed for the patient to attempt to modify the diet to achieve the desired goals of therapy.

Dietary Therapy for Special Groups

Severe Primary and Secondary Lipid Disorders.—Patients with severe primary hypercholesterolemia (eg, familial hypercholesterolemia) deserve maximal dietary therapy, ie, the Step-Two Diet. However, many of these patients will not respond adequately to diet and will require drug therapy (see Appendix II). Patients with severe primary hypertriglyceridemia should receive special attention to dietary management, which is described in more detail in Appendix II. The role of the diet in the treatment of low HDL-cholesterol and diabetic dyslipidemia likewise is discussed in Appendix II.

Elderly High-Risk Patients.—When considering dietary therapy for elderly patients classified as high risk, the value of diet modification for prevention of atherosclerotic disease must be balanced against the possibility of inadequate or inappropriate nutrition, which is often a problem in the elderly. The Step-One Diet seems prudent in elderly patients classified as high risk, but overly restrictive diets probably should be avoided. Intensive dietary therapy (eg, the Step-Two Diet) is not advisable in most elderly patients. Sound clinical judgment is required in making a decision about diet modification in older individuals classified as high risk, particularly because adequate intakes of calories and protein can be a major problem among the elderly.

Pregnant Women.—Elevations in cholesterol and triglyceride levels occur during pregnancy, with maximum levels in the third trimester. These increased levels are not generally clinically significant, but rare cases of hypertriglyceridemia and pancreatitis have been reported. Thus, some investigators recommend that serum triglyceride levels be measured at about the 28th week of gestation. Triglyceride levels generally return to baseline within six weeks postpartum, but elevations in LDL-cholesterol may occasionally persist for six to nine months. Such a response may represent a predisposition to elevated cholesterol. The approach to hyperlipidemic women who become pregnant is discussed in Appendix II.

Approach to Borderline–High Blood Cholesterol Group

Assessment of Risk.—Individuals with cholesterol levels in the range of 200 to 239 mg/dL are classified as having borderline–high blood cholesterol. Several studies indicate that cholesterol concentrations in the borderline-high range impart an increased CHD risk as compared with lower levels. However, while there is a progressive increase in risk as the blood cholesterol level rises from 200 to 240 mg/dL, the absolute risk does not rise sharply if no other risk factors are present (Table 3, "Background section"). For this reason, it is not necessary to enter most

people with borderline-high b... cholesterol into active medical therapy. They nonetheless deserve to receive dietary information and cholesterol education as discussed below.

Special attention should be given to young adults with borderline-high blood cholesterol because they may be "tracking" toward the high-risk category later in life. In fact, many experts believe that young adults (20 to 39 years of age) with borderline-high blood cholesterol levels warrant full evaluation of serum lipoprotein fractions. This is an area where individualized clinical judgment is appropriate.

As with all patients, those with borderline-high blood cholesterol levels should be evaluated for other CHD risk factors and should be given preventive medical care for these factors if present. As indicated previously, patients in the borderline-high blood cholesterol group who have definite CHD or two other CHD risk factors (one of which can be male sex) should be managed in the same way as patients with high blood cholesterol levels.

Some experts believe that patients in the borderline-high blood cholesterol group who have one other major risk factor (eg, hypertension) also warrant lipoprotein measurements and possible dietary therapy. This is particularly so for young adults. Although this is not recommended here as a general approach for most patients with borderline-high blood cholesterol, it is clear that individualized clinical judgment and patient management is appropriate for this group.

Dietary Information and Patient Education.—For individuals with borderline-high blood cholesterol, intensive dietary therapy is not required. The population-based approach for lowering cholesterol levels in the entire community is expected, however, to have a significant impact on the diet and behavior of this group. Since these people are at increased risk for CHD, compared with individuals whose cholesterol levels are below 200 mg/dL, they should be made aware of the significance of their moderately increased risk and given information about how to modify the diet to lower the cholesterol level. The basic recommendation is for the patient to adopt an eating pattern similar to that of the Step-One Diet.

The same materials provided with the Step-One Diet might be made available to these patients by the physician and immediate staff, but intensive monitoring is not required. It should not be necessary to refer the patient to a registered dietitian, and the time devoted to patient instruction will be less than for the high-risk group. It is the physician's responsibility to inform the patient of his or her moderately increased risk, to advise changes in life-style and eating habits, to provide educational materials about diet, and to direct the individual to other sources of educational material. For instance, the local chapter of the American Heart Association usually stocks valuable materials containing dietary advice and practical approaches to diet modification. Sections of this report also can be copied for the patient.

Special attention should be given to dietary counseling of young adults with borderline-high blood cholesterol levels. They should be started on the Step-One Diet, but, in addition, they should be monitored for adherence and response more carefully than middle-aged patients in the same category. Young adults should be counseled on what to eat when away from home, and they should develop exercise habits that will be particularly useful as lifetime habits. Young adults who have an exceptionally high caloric intake because of a high level of exercise should be cautioned against excessive intake of saturated fatty acids, cholesterol, and protein.

Reevaluation.—At the least, a follow-up measurement of the patient's cholesterol level should be made at one year and then at one- to two-year intervals. More frequent followup or measurements of lipoprotein fractions can be made at the discretion of the physician. Extra attention should be given to the followup of young adults with borderline-high blood cholesterol. Periodic determinations of serum cholesterol will indicate the physician's heightened and continuing concern; knowledge that the cholesterol level will be checked periodically should motivate the patient to adhere to the recommended diet; and these measurements will enable the physician to detect an increase in cholesterol level to the high blood cholesterol range, should it occur.

DRUG TREATMENT

When to Consider Drug Therapy/Treatment Goals

LDL-Cholesterol Levels for Initiation of Drug Therapy.—Patients whose LDL-cholesterol levels remain high despite adequate dietary therapy should be considered for drug treatment. At least six months of intensive dietary therapy and counseling should usually be carried out before initiating drug therapy. In individuals with severe elevations of LDL-cholesterol (>225 mg/dL) or with definite CHD, in whom dietary therapy alone is unlikely to be adequate or in whom the urgency of achieving substantial cholesterol lowering is greater, it may be appropriate to try dietary therapy alone for a period shorter than six months before considering drug therapy. A minimum of three months of dietary therapy is required to establish an adequate baseline for evaluating the efficacy of subsequent drug therapy. A registered dietitian, working with the physician to design an adequate treatment plan and assess dietary adherence, may enhance the effectiveness of dietary therapy sufficiently to obviate the need for drugs.

The LDL-cholesterol levels at which drug therapy should be considered after an adequate trial of dietary therapy alone are as follows:

(1) ≥190 mg/dL (very-high-risk LDL-cholesterol) in patients without definite CHD or two other CHD risk factors, one of which can be male sex (Table 4).

(2) ≥160 mg/dL (high-risk LDL-cholesterol) in patients with definite CHD or two other CHD risk factors (Table 4).

Clinical judgment is required when using these guidelines to make decisions about initiating drug therapy. All individuals with LDL-cholesterol levels ≥190 mg/dL are candidates for drug therapy, but the need is less pressing in older women. Men with LDL-cholesterol values between 160 and 190 mg/dL who have any other major risk factor generally should receive drug therapy. In women, however, a more conservative approach to drug therapy is appropriate, in view of the fact that the absolute risk of CHD is lower in women than in men. Thus, for women with LDL-cholesterol levels between 160 and 190 mg/dL, two other major risk factors or definite CHD should be present before initiating drug therapy. The distribution of LDL-cholesterol levels in the population is listed in Appendix I. It should be emphasized that maximum dietary therapy would significantly alter this distribution and decrease the percent of both men and women being considered for drug therapy.

Maximal efforts should be made in all patients to lower cholesterol levels and CHD risk by nonpharmacological approaches, such as diet, weight control, exercise, and other life-style modifications (eg, quitting smoking). This is especially important in patients who have not reached

Table 9.—Summary of the Major Drugs for Consideration*.

Drugs	Reduce CHD Risk	Long-term Safety	Maintaining Adherence	LDL-Cholesterol Lowering, %	Special Precautions
Cholestyramine, colestipol	Yes	Yes	Requires considerable education	15-30	Can alter absorption of other drugs, can increase triglyceride levels and should not be used in patients with hypertriglyceridemia
Nicotinic acid	Yes	Yes	Requires considerable education	15-30	Test for hyperuricemia, hyperglycemia, and liver function abnormalities
Lovastatin†	Not proven	Not established	Relatively easy	25-45	Monitor for liver function abnormalities, and possible lens opacities
Gemfibrozil‡	Not proven	Preliminary evidence	Relatively easy	5-15	May increase LDL-cholesterol in hypertrigtyceridemic patients; should not be used in patients with gallbladder disease
Probucol	Not proven	Not established	Relatively easy	10-15	Lowers HDL-cholesterol; significance of this has not been established; prolongs QT interval

*CHD indicates coronary heart disease; LDL, low density lipoprotein; and HDL, high density lipoprotein.
†Recently approved by the Food and Drug Administration for marketing.
‡Not approved by the Food and Drug Administration for routine use in lowering cholesterol. The results of the Helsinki Heart Study should be available soon to define the effect on CHD risk and long-term safety.

their minimal LDL-cholesterol goal on dietary therapy alone, but who do not qualify for drug treatment according to the above guidelines. These patients include those without definite CHD or two other risk factors (see Table 4), whose LDL-cholesterol levels are in the range of 160 to 190 mg/dL, and those with definite CHD or two other risk factors, whose LDL-cholesterol levels are 130 to 160 mg/dL, on adequate dietary therapy. While drug therapy is not routinely recommended for such patients, consideration should be given to the use of low doses of bile acid sequestrants, especially in men. The sequestrants have a proven record of long-term safety. Moreover, many experts feel that patients with definite CHD should receive drug therapy if their minimal LDL-cholesterol goal (<130 mg/dL) has not been reached.

Low density lipoprotein–cholesterol is the best parameter to use in making the decision to use drugs and for monitoring the response to drug therapy (at least in the first few months). The decision to initiate drug treatment usually commits the patients to long-term therapy, for years or even for life. Since the number of potential patients who are candidates for prolonged administration of drugs is substantial, all decisions to initiate drug therapy must be made only after careful deliberation. Dietary therapy is clearly the safest treatment available. Hence, maximal efforts at dietary therapy should be made before initiating drug therapy, and should be continued even if drug therapy is needed. (For detailed information about the effects of drugs on serum lipids and lipoproteins and on CHD risk, including key studies and reviews, the reader should consult references 7, 10-13, and 50-60.)

Target Treatment Levels of LDL-Cholesterol.—The minimum goals of drug therapy are the same as those of dietary therapy, and are as follows:

(1) LDL-cholesterol <160 mg/dL in patients without definite CHD or two other CHD risk factors (one of which can be male sex, [Table 4]).

(2) LDL-cholesterol <130 mg/dL in patients with definite CHD or two other CHD risk factors (Table 4).

The LDL-cholesterol level that is necessary to promote substantial or maximal atherosclerotic regression has not been established, but some investigators believe that an LDL-cholesterol level as low as 100 mg/dL may be considered an ideal goal. Thus, it may be desirable to strive for an LDL-cholesterol level considerably below the minimal target goals of 160 mg/dL or 130 mg/dL, particularly in patients with definite CHD or with other major risk factors, once the decision to institute drug therapy has been made. There is no current evidence or opinion to suggest that further lowering of LDL-cholesterol below 100 mg/dL will produce significant additional benefit.

Selection and Use of Drugs

Overview and General Approach.—The major drugs for consideration include the following: bile acid sequestrants (cholestyramine, colestipol); nicotinic acid; HMG CoA reductase inhibitors (lovastatin); gemfibrozil; and probucol.

A brief summary of the major characteristics of these drugs is provided in Tables 9 and 10.

The drugs of first choice for patients without concurrent hypertriglyceridemia (triglyceride, <250 mg/dL) are the bile acid sequestrants and nicotinic acid. These drugs have been found to reduce CHD risk and to be generally safe in long-term use. They are effective in lowering LDL-cholesterol. Nicotinic acid is preferred for patients with concurrent hypertriglyceridemia (triglyceride, ≥250 mg/dL), because it lowers LDL-cholesterol without exacerbating the hypertriglyceridemia. The bile acid sequestrants can also effectively lower LDL-cholesterol in these patients, but their administration as single drug therapy will sometimes cause substantial increases in serum triglycerides.

Lovastatin is the first available drug in a new class, the HMG CoA reductase inhibitors. It is very effective in lowering LDL-cholesterol levels, produces modest reductions in triglyceride levels, and is easy to administer. The clinical use of lovastatin has been under study for only a few years, and its long-term safety and effects on CHD end points have not yet been established. It is, therefore, not classed as a drug of first choice in this report, and some caution is appropriate in its use.

Gemfibrozil and probucol are other available drugs that are also not classified as drugs of first choice. These drugs are generally not as effective in lowering LDL-cholesterol as are the bile acid sequestrants, nicotinic acid, or the

Table 10.—Drugs Highly Effective in Lowering LDL-Cholesterol*

Drug	Starting Dose	Maximum Dose	Usual Time and Frequency	Side Effects	Monitoring
Cholestyramine, colestipol	4 g twice daily, 5 g twice daily	24 g/d, 30 g/d	Twice daily within an hour of major meals	Dose-dependent upper and lower gastrointestinal tract	Dosing schedules of coadministered drugs
Nicotinic acid	100-250 mg as single dose	3 g/d, rarely doses up to 6 g are used	Three times a day with meals to minimize flushing	Flushing, upper gastrointestinal tract and hepatic	Uric acid, liver function, glucose
Lovastatin	20 mg once daily with evening meal	80 mg/d	Once (evening) or twice daily with meals	Gastrointestinal tract and hepatic, miscellaneous, including muscle pain	Liver function, creatine kinase, lens

*LDL indicates low density lipoprotein.

HMG CoA reductase inhibitors. Moreover, these drugs have not been shown to reduce CHD risk and their safety for long-term use has not been established at this time. However, the results of a large clinical trial, the Helsinki Heart Study, evaluating the effects of gemfibrozil on CHD risk are expected soon.[29] If a clinically beneficial effect is seen, the recommended use of gemfibrozil will probably be expanded.

The cost of drugs may also warrant consideration. Cost should be viewed in relation to a drug's effectiveness and safety in cholesterol lowering. The following are the approximate yearly wholesale costs of drugs, derived from data in the 1986 Redbook; retail costs will be somewhat higher. Cholestyramine (Questran) at a daily dose of 16 g or colestipol (Colestid) at a daily dose of 20 g in bulk containers is $500 to $550; "generic" nicotinic acid at a daily dose of 3 g is $50, while Nico-Bid is $700; gemfibrozil (Lopid) at a daily dose of 1.2 g or probucol (Lorelco) at a daily dose of 1 g is approximately $375. Lovastatin is being marketed to the pharmacist at $1.25 per 20-mg tablet; at a dose of 40 mg/d, the yearly wholesale cost will be approximately $910.

Many patients with marked elevations of LDL-cholesterol will not be adequately controlled with single-drug therapy, and the use of combinations of drugs with synergistic mechanisms of action may be particularly effective in these patients. The mechanisms of action, clinical efficacy, and side effects of the drugs of first choice and the HMG CoA reductase inhibitors for the treatment of high-risk LDL-cholesterol levels are discussed in the following section. There then follows a more abbreviated discussion of the other drugs and of combination drug therapy.

Drugs of First Choice.—*Bile Acid Sequestrants: Cholestyramine and Colestipol.*—The major effect of the bile acid sequestrants is a lowering of the level of LDL-cholesterol. The sequestrants have the advantage that their use has been shown to reduce CHD risk in large-scale intervention trials and that long-term safety information is also available.[15,16] The sequestrants are not absorbed from the gastrointestinal tract and lack systemic toxicity. Thus, they are particularly suitable for treating younger patients, especially children and women considering pregnancy. The disadvantages of the sequestrants are related to the method of administration and the frequency of gastrointestinal side effects.

The primary action of the sequestrants, which are anion exchange resins, is to bind bile acids in the intestinal lumen; this interrupts the enterohepatic circulation of bile acids and leads to an increased hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in LDL receptor activity in the liver. This in turn stimulates removal of LDL from plasma and lowers the concentration of LDL-cholesterol. Bile acid sequestrant therapy may increase hepatic VLDL production and thus increase the plasma concentration of triglycerides.

Cholestyramine and colestipol are both powders that must be mixed with water or fruit juice; they are taken in two (or, occasionally, three) divided doses with meals. The cholesterol-lowering effects of 4 g of cholestyramine are equivalent to those obtained with 5 g of colestipol. Decreases in LDL-cholesterol of 10% to 15% may be achieved with the initial suggested starting dosage schedule of 5 g of colestipol (or 4 g of cholestyramine) taken twice daily. In patients who do not respond adequately, the dose is increased gradually. Generally, the benefits of daily doses exceeding the equivalent of 16 g of cholestyramine are offset by poorer patient adherence and a greater incidence of gastrointestinal side effects. The response to therapy in individual patients is quite variable, but 15% to 30% reductions in the concentrations of LDL-cholesterol may be achieved with 16 to 24 g/d of cholestyramine or an equivalent dose of colestipol. The choice of one or the other of these drugs is dependent on individual patient preference based on taste and palatability. Cholestyramine is available in 9-g packets (each containing 4 g of cholestyramine and 5 g of orange-flavored filler) and in 378-g cans. Colestipol is available in 5-g packets and bottles containing 500 g, and there are no additives. The cost-per-unit dosage for cholestyramine is currently considerably less when it is purchased in bulk containers.

The bile acid sequestrants are contraindicated as single-drug therapy in patients with marked hypertriglyceridemia (triglyceride, >500 mg/dL) or patients with a history of severe constipation. The most common side effects associated with sequestrant therapy are gastrointestinal, and include constipation, bloating, epigastric fullness, nausea, and flatulence. Some suggestions for dealing with these side effects are provided in Appendix IV. These drugs are not absorbed, but they may interfere with the absorption of other anionic drugs if these are taken concurrently. It is generally advisable to take other medications at least one hour before or four hours after the bile acid sequestrants. The sequestrants can interfere with the absorption of digitoxin, warfarin, thyroxine, thiazide diuretics, beta blockers, and, potentially, many other drugs. Decreased absorption of fat-soluble vitamins and folic acid has been reported with prolonged high doses of the resins, primarily in patients with severe liver or small-bowel disease. Routine vitamin supplementation is not needed or recom-

mended in adult patients. Biochemical side effects include a modest increase in plasma triglyceride concentrations in many patients and an occasional mild and usually transient increase in alkaline phosphatase and transaminase.

Nicotinic Acid.—The water-soluble B vitamin, nicotinic acid, has been used to lower plasma lipid levels for many years. Administration of nicotinic acid in the Coronary Drug Project was associated with a reduction in recurrent myocardial infarctions and in long-term total mortality.[11,53] Nicotinic acid lowers total and LDL-cholesterol and triglyceride levels and raises HDL-cholesterol levels. Decreases in total cholesterol levels of 25% may be observed. Nicotinic acid decreases the hepatic production of VLDL and, ultimately, the production of LDL-cholesterol. Nicotinamide is not effective in lowering LDL-cholesterol and cannot substitute for nicotinic acid.

Nicotinic acid is a very effective drug that requires considerable physician and patient education (Appendix IV). Although it has frequent side effects, these are generally reversible on reducing the dose or discontinuing the drug. Because of its proven efficacy and safety, the efforts required to use this agent are justified.

Nicotinic acid is the least costly of all the currently available agents. Side effects, especially flushing of the skin, often limit acceptance by patients. The flushing is prostaglandin mediated and can be significantly decreased by pretreatment with aspirin or nonsteroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over several weeks. Flushing is greatly reduced by slowly increasing the dose of nicotinic acid and avoiding administration on an empty stomach. The use of sustained-release preparations will also reduce flushing, but the cost is considerably greater.* Flushing will return if doses are omitted from the prescribed schedule.

Nicotinic acid therapy is generally initiated with a single dose of 100 to 250 mg/d. This initial dose is usually given after dinner to minimize problems with flushing during normal daily activities. The frequency of dose and total daily dose is slowly increased every four to seven days until the first-level therapeutic dose of 1.5 to 2 g/d is reached. If the LDL-cholesterol is not lowered sufficiently, the dose should be increased to 3 g/d (1.0 g three times per day). In patients with marked elevations of plasma cholesterol, a higher daily dose up to 6 g/d is occasionally used.

Hyperuricemia and abnormalities in liver function studies are other common adverse effects, but are more likely with higher doses of nicotonic acid. Hyperglycemia and a number of gastrointestinal side effects occasionally occur. Liver function, blood glucose, and uric acid levels should be evaluated before beginning nicotinic acid and after reaching therapeutic dosage or increasing the dose level. The medication is supplied in 50-, 100-, and 500-mg tablets. The latter dosage is preferred for chronic therapy. Contraindications to nicotinic acid therapy include peptic ulcer, hepatic disease, and gouty arthritis or significant hyperuricemia.

New Drugs: Inhibitors of HMG CoA Reductase.—The discovery of specific competitive inhibitors of the rate-limiting enzyme in cholesterol biosynthesis (HMG CoA reductase) has opened up a new avenue of therapy for patients with primary hypercholesterolemia.**** A number of drugs in this category are currently being evaluated including lovastatin, simvastatin, and pravastatin. Of these, lovastatin has been most extensively studied in humans and has recently been approved for marketing. Long-term safety information is limited or not available, and thus caution in its use is recommended. This is especially true for individuals who are not at high risk.

Although the effects of HMG CoA reductase inhibitors on CHD incidence have not yet been established, mean reductions in LDL-cholesterol of 25% to 45% have been noted in both familial and nonfamilial forms of hypercholesterolemia. The HMG CoA reductase inhibitors increase LDL receptor activity in the liver and increase the rate of receptor-mediated removal of LDL from plasma. Additionally, the production of LDL is also decreased. Patients are generally started on 20 mg of lovastatin once daily with the evening meal. The dose may be increased to 40 and then to 80 mg/d as a single evening dose or divided (twice a day) doses with meals. The cholesterol-lowering effects of lovastatin have persisted for the duration of the observed treatment periods up to two to four years.

Lovastatin at doses of 20 to 80 mg daily has been well tolerated. Reported side effects (often transient) to date have included changes in bowel function, headaches, nausea, fatigue, insomnia, skin rashes, and myositis (myalgia associated with markedly elevated creatine kinase [CPK] levels), which collectively have occurred in less than 5% of treated patients. Biochemical changes have included increases in transaminase and CPK levels. Approximately 1.2% of patients have developed persistent increases in transaminase levels of greater than three times normal after three to 16 months of therapy, requiring discontinuance of therapy. Careful monitoring of liver function studies is essential. Lovastatin does not impair steroid hormone production. There is a concern about the possibility that there may be effects on formation of lens opacities; although no effects have been detected to date in humans, this is still being investigated. Baseline and regular follow-up evaluation of the lens should be done.

If long-term safety can be satisfactorily established, these inhibitors of cholesterol biosynthesis will represent a major advance in the therapy of hypercholesterolemia. These agents are extremely effective in reducing LDL-cholesterol concentrations and, from the patient's point of view, are easy to take.

Other Drugs.—*Gemfibrozil.*—Gemfibrozil, a fibric acid derivative, is approved by the Food and Drug Administration primarily for triglyceride lowering to reduce the risk of pancreatitis, and not for routine use in lowering cholesterol to reduce the risk of CHD. It is sometimes used as single drug therapy in patients who do not tolerate the resins or nicotinic acid, and is occasionally used in combination with first-choice drugs (see the section on "Combined Drug Treatment"). The long-term safety and effects of gemfibrozil on CHD risk are still being evaluated in clinical trials. Preliminary evidence for long-term safety of gemfibrozil is available in the interim report of the Helsinki Heart Study.* This is a large, placebo-controlled study to evaluate the effect of this drug on CHD risk, and the results should be announced in the near future. If a clinically beneficial effect is demonstrated in this clinical trial, the recommended use of gemfibrozil will probably be expanded.

Gemfibrozil is primarily and highly effective in lowering triglycerides, and there is an associated increase in HDL-cholesterol. Because of the effect of this drug on HDL-cholesterol, the results of the Helsinki Heart Study may be of particular interest. To date, increases of HDL-cholesterol induced by treatment have not been conclusively shown to be associated with a decreased risk of CHD. A decrease in LDL-cholesterol of 10% to 15% may be seen in patients without elevated triglycerides treated with gemfibrozil. An increase in LDL-cholesterol may be seen in primary hypertriglyceridemia, and either increases or decreases in LDL-cholesterol may be seen in patients

with elevated levels of both cho...rol and triglycerides. Gemfibrozil is well tolerated in most patients. The more common side effects include a variety of gastrointestinal symptoms, and occasional changes in hematologic parameters and liver function tests are noted. Gemfibrozil does potentiate the effects of oral anticoagulants and increases biliary lithogenicity. It is available as 300-mg capsules, and the usual dosage is 600 mg twice daily.*

Probucol.—Probucol therapy usually reduces LDL-cholesterol by about 8% to 15%, but there is also an associated reduction in HDL-cholesterol of up to 25%. There are no extensive, long-term clinical studies currently available for assessing probucol's safety or effect on CHD risk. Preliminary information indicates that probucol may inhibit the oxidation and tissue deposition of LDL. Probucol increases the rate of LDL catabolism, part of which may involve nonreceptor-mediated pathways.[87] The role of probucol in the treatment of patients with high LDL-cholesterol is uncertain because of concerns about the reduction in HDL-cholesterol, but xanthoma regression has also been reported as the HDL-cholesterol level decreases. Probucol is sometimes used as single drug therapy in patients who do not tolerate other drugs, and is occasionally used in combination with first-choice drugs (see the section on "Combined Drug Treatment").

Probucol is generally well tolerated, and side effects (including diarrhea, flatulence, abdominal pain, and nausea) occur in less than 5% of patients. Probucol causes prolongation of the QT interval, and the drug should be regarded as contraindicated in patients with electrocardiographic findings suggestive of ventricular irritability, with an initially prolonged QT interval, or taking other drugs that prolong the QT interval. Probucol is stored in adipose tissue, and blood levels fall slowly after therapy is discontinued. It is available in 250-mg tablets, and the usual dose is 500 mg twice daily.

Clofibrate.—Clofibrate, like gemfibrozil, is a fibric acid derivative. It is approved by the Food and Drug Administration primarily for triglyceride lowering to reduce the risk of pancreatitis, and not for routine use in lowering cholesterol to reduce the risk of CHD. Its effects on lipids and lipoproteins and its side effects are generally similar to those described above for gemfibrozil. Clofibrate is used less frequently than gemfibrozil, however, because of reports of long-term toxicity in clinical trials, particularly the World Health Organization Clofibrate Study.[88]

*Additional Note: The following statement was prepared by the Steering Committee of the Cholesterol Adult Treatment Panel (Drs Goodman, Cleeman, Brown, Grundy, Hulley, Hunninghake, and Rifkind) six weeks following the final approval of the report by the National Cholesterol Education Program Coordinating Committee:

Subsequent to the formal endorsement of this report by the National Cholesterol Education Program Coordinating Committee, the results of the Helsinki Heart Study were reported (Frick, MH, et al, *N Engl J Med* 1987;317:1237-1245). This randomized, double-blind five-year trial tested the clinical efficacy and safety of gemfibrozil, 600 mg twice daily, vs placebo in 4081 asymptomatic middle-aged men with elevated blood cholesterol levels. Gemfibrozil moderately reduced the serum levels of total and LDL-cholesterol, and also reduced triglycerides and increased HDL-cholesterol levels. The incidence of CHD was reduced by 34% in the drug-treated group ($P<.02$). This trial thus demonstrates the clinical efficacy and safety of gemfibrozil in reducing coronary risk in patients with high cholesterol levels. In view of these results, it would be reasonable for physicians to consider the use of gemfibrozil more readily when selecting drugs for patients with high cholesterol levels who meet the criteria for drug treatment. Gemfibrozil may be particularly useful, as an alternative to nicotinic acid, in patients with high-risk LDL-cholesterol levels who also have borderline hypertriglyceridemia (triglyceride levels, 250 to 600 mg/dL) and low HDL-cholesterol levels. More extensive review and evaluation of the results of the Helsinki Heart Study may further clarify the place of gemfibrozil in the treatment of patients with high blood cholesterol.

Miscellaneous Drugs.—These drugs are not recommended for general use.

Neomycin.—Neomycin is a nonabsorbable aminoglycoside antibiotic with cholesterol-lowering effects. Reductions in LDL-cholesterol levels of 20% to 25% have been reported. Side effects include diarrhea and abdominal cramps. Neomycin also has a potential to cause serious ototoxicity and nephrotoxicity. This drug is not approved by the Food and Drug Administration as a lipid-lowering agent, and its use should be considered investigational.

Dextrothyroxine.—Dextrothyroxine, the optical isomer of L-thyroxine, moderately lowers the concentrations of LDL-cholesterol, but does so at the expense of making the patient moderately hyperthyroid. Dextrothyroxine is approved by the Food and Drug Administration for use in selected young adults with primary hypercholesterolemia who are unable to take other effective lipid-lowering drugs. It is not recommended for use in this report because of the high incidence of adverse cardiovascular effects and hypermetabolic effects. Other available drugs have a more favorable benefit/risk ratio.

Investigational Drugs.—There is currently a flurry of activity in the development of new cholesterol-lowering agents. There are several new HMG CoA reductase inhibitors in various stages of development. Simvastatin and pravastatin are currently being extensively investigated in clinical trials. A number of newer fibric acid derivatives are available in Europe, and bezafibrate and fenofibrate have been fairly extensively evaluated in the United States. They appear to be more effective in lowering LDL-cholesterol than gemfibrozil or clofibrate.

Combined Drug Treatment.—If the response to single-drug therapy with one of the drugs of first choice is inadequate, combined drug therapy using two agents, preferably with synergistic mechanisms of action, should be considered to further lower LDL-cholesterol.[12,56,60] Experience with such drug combinations is somewhat limited, and it might be advisable to undertake such combination therapy in consultation with a lipid specialist. In patients without concurrent hypertriglyceridemia, the combination of a bile acid sequestrant with either nicotinic acid or lovastatin has the potential of lowering LDL-cholesterol by 45% to 60%. The addition of probucol or gemfibrozil to bile acid sequestrant therapy may occasionally be beneficial, but the efficacy of these combinations is significantly less than the abovementioned combinations. The combination of sequestrants and probucol may result in fewer gastrointestinal complaints.

For patients with both increased LDL-cholesterol levels and hypertriglyceridemia, nicotinic acid and lovastatin represent initial drugs of choice. Lovastatin and nicotinic acid can also be used in combination, or either of these two drugs can be combined with a bile acid sequestrant to obtain a possible additional 20% to 25% reduction in LDL-cholesterol. As yet, there is very little experience with the combination of lovastatin and nicotinic acid in terms of possible adverse effects such as hepatotoxicity. The addition of gemfibrozil to a bile acid sequestrant, lovastatin, or nicotinic acid will usually produce additional lowering of triglycerides, but the effect on change in LDL-cholesterol levels is quite variable. More experience is required with the combination of lovastatin and gemfibrozil to see if there is an increased risk of myositis.

Other Approaches.—Effective control of elevated levels of LDL-cholesterol will be attainable in the majority of patients using the primary drugs and drug combinations discussed above. Patients who do not achieve adequate cholesterol reduction after this type of therapy should be

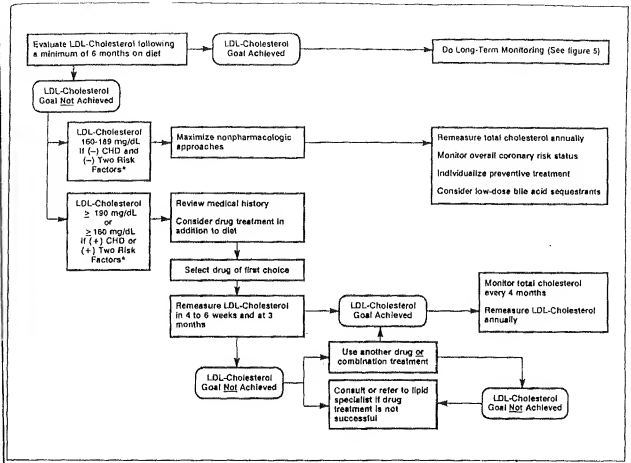

Fig 6.—Drug treatment. Asterisk indicates one of which can be male sex (Table 4); LDL, low density lipoprotein; CHD, coronary heart disease.

referred to a specialist in lipid disorders. In addition to investigational drugs or other drug combinations, other approaches may be indicated. In patients with FH, plasmapheresis (either simple plasma exchange or plasma exchange with some type of affinity chromatography) has been used to selectively remove LDL from plasma. A surgical procedure, partial ileal bypass, has occasionally been used to lower LDL-cholesterol in heterozygous FH. In homozygous FH, portacaval shunt and liver transplant have been employed.

Monitoring and Followup of Patients

Drug therapy is usually not begun until patients have had at least a six-month trial of dietary therapy. The decision to begin drug therapy should be reviewed with the patient along with the respective benefits and side effects of the appropriate drugs.

It is important to have a minimum of two determinations of lipoprotein levels during the last one to two months of maximum dietary therapy, because the efficacy of drug therapy needs to be judged against an accurately determined baseline. With good drug adherence, maximum lowering of LDL-cholesterol is obtained within four weeks of initating drug therapy. Thus, the first follow-up LDL-cholesterol determination should be made four to six weeks after initiating drug therapy. A second measurement should be done at three months; a minimum of two lipoprotein determinations is essential for evaluating drug efficacy. The mean of these two determinations and a careful assessment of drug adherence should be used to initially judge the effectiveness of drug treatment. After the response to drug therapy has been established and if the response is adequate, then the patient should be seen for a follow-up visit approximately every four months, in order to monitor for side effects and assess the patient's status and response to therapy. A lipoprotein profile (LDL-cholesterol measurement) at yearly intervals will usually be adequate; measurement of serum total cholesterol will usually suffice for the interim visits (Fig 6). In the course of long-term monitoring, if the total cholesterol or lipoprotein determination at a particular visit is out of keeping with the patient's previous values, the determination should be repeated to confirm the level.

The previously obtained laboratory work and medical history and physical examination should be reviewed before initiating drug therapy to see if any tests should be repeated or whether additional tests are required. The laboratory indications of adverse drug effects are generally manifested by changes in blood count, or liver or kidney function studies. These tests should definitely be repeated within one to three months of initiation of drug therapy, depending on the drug used, and at four- to 12-month

intervals thereafter. Additional testing may be required if abnormalities are noted, or if a high dose of drug is being used, or because of the known toxicity profile of a given drug (see previous discussion of major adverse effects for individual drugs). For example, more frequent transaminases are indicated when using lovastatin and more frequent uric acid and liver function determinations with higher doses of nicotinic acid.

The use of the bile acid sequestrants and nicotinic acid requires frequent observation or contact with the patient during the early stage of treatment. Clinic visits and/or telephone contact is usually indicated at least at monthly intervals for three to four months. Lovastatin requires continuing liver function and lens evaluation. Thus, there is a need for judgment regarding the frequency of visits and observation during the early phases of drug therapy. When the final drug regimen has been established, follow-up visits should continue at four-month intervals to promote adherence. Many of the routine patient contacts may not need direct physician involvement but may be handled instead by physician's assistants, nurses, pharmacists, or dietitians.

If the patient has had at least a 15% decrease in LDL-cholesterol and is tolerating the drug but has not achieved the minimal target goal for LDL-cholesterol, consideration should be given to adding another drug as discussed in the "Combined Drug Treatment" section. If the patient has not had a 15% decrease in LDL-cholesterol or is not tolerating the drug, the physician should either switch to another drug or proceed to combination therapy, if necessary. Consultation with a lipid specialist may be useful in the management of patients with persistently high LDL-cholesterol levels despite dietary and drug therapy.

Adherence to Drug Therapy

General Comments.—Drug therapy is likely to continue for a lifetime or for a very prolonged period of time. Hence, the patient must be well informed about the goals of drug treatment and the side effects of medication. The need for a long-term commitment must be emphasized. When dealing with the selection of bile acid sequestrants vs newer, "easier" drugs, safety must be emphasized. It is important to start with small doses of the drugs, especially when using sequestrants and nicotinic acid. The patient must have time to adapt to the drug regimen, and any difficulties must be remedied before proceeding to higher doses. Health professionals who are already involved in patient education would be a logical source of help for the patient who is having problems with side effects. The initial experience with a regimen is likely to predict long-term adherence.

The frequency of medication intake and its impact on life-style must be frankly discussed. The planned regimen should attempt to minimize changes in daily life-style. Reinforcement of adherence by periodic laboratory monitoring and reassurance is essential. There is also a need for patience, an adequate amount of time, and understanding on the part of the health professional. It must be emphasized to patients that the ultimate responsibility for management is theirs, and communication with the appropriate health professional is essential when problems arise. The importance of diet in addition to drugs must continue to be emphasized. Some practical suggestions concerning adherence are summarized in Appendix IV.

Patient Counseling/Assessment of Adherence.—The management of a risk factor like elevated serum cholesterol is multifactorial and in the ideal treatment setting would call on the expertise of a variety of professionals. Time and resources dictate a more prudent approach. Drug therapy for many patients can be successfully managed by the physician in his or her office along with the assistance of an office health professional who has skill and experience in teaching patients and some understanding of the side effects of drugs and approaches to their management. This person will generally be a nurse, or a nursing or physician's assistant. The community pharmacist is also a valuable resource for patient education. Additional educational efforts are usually required to ensure the successful utilization of the bile acid sequestrants and nicotinic acid, as compared with the other cholesterol-lowering drugs. There should be regular communication with the supervising physician, but many other health professionals can effectively educate the patient. A sensitive, caring individual who routinely sees the patient (constant caretaker model) and develops the patient's trust is often an important component of an effective adherence counseling program.

It is important that community health care providers utilize appropriate specialist consultation. Lipid specialists are available in most large metropolitan areas. Of major importance is the maintenance of continuing education in the cholesterol area, where knowledge is rapidly growing. Furthermore, consultation on an ongoing basis may be sought so that more difficult cases or situations can be reviewed and consultation obtained for planning treatment. If the target treatment goals for LDL-cholesterol are not achieved or if the patient is having considerable problems with side effects of medication, referral to a specialist in lipid disorders may be indicated. This is especially important if the patient has definite CHD, a genetic disorder with severe hypercholesterolemia, or other major risk factors. It is difficult to provide the best care possible through the use of a multidisciplinary team and also control the cost of treatment to the patient. Minimizing the number of office visits, limiting the number of direct care providers, and using the least costly provider with the broadest skills for routine care will help. Maximizing the response to dietary therapy will minimize the need for costly drug therapy. The use of standardized teaching materials that can be adapted to individual needs, and inexpensive follow-up between office visits (eg, telephone or postcard exchanges) may help patients successfully follow a regimen that has been tailored to their circumstances and that has every likelihood of effectively lowering their elevated cholesterol levels.

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APPENDIXES

Appendix I

Table I—Corresponding Levels of Lipids*

Cholesterol		Triglyceride	
mg/dL	mmol/L	mg/dL	mmol/L
35	0.9	250	2.8
130	3.4	400	4.5
160	4.1	500	5.6
190	4.9	1000	11.3
200	5.2	. . .	. . .
240	6.2	. . .	. . .

Table 1-2.—Mean Serum Cholesterol Levels of Men and Women, SEM, Age-Adjusted Means, Selected Percentiles, Number of Examined Persons, and Estimated Population, by Race and Age: United States, 1978-1980

Race, Age, y	No. of Persons Examined	Estimated Population in Thousands	Mean	SEM	Percentile*								
					5th	10th	15th	25th	50th	75th	85th	90th	95th
Men													
All races†													
20-74	5604	63611	211	1.2	144	156	165	179	206	239	258	271	291
20-24	676	9331	180	1.7	129	136	145	155	176	202	215	227	246
25-34	1067	15895	199	1.5	141	152	159	172	194	220	240	254	275
35-44	745	11367	217	2.0	153	166	173	187	215	244	262	275	293
45-54	690	11114	227	1.8	159	176	182	197	223	255	271	283	303
55-64	1227	9607	229	1.8	164	176	184	198	225	254	277	288	307
65-74	1199	6297	221	1.8	153	167	175	191	217	249	265	279	301
White													
20-74	4883	55808	211	1.2	145	157	166	179	207	239	258	271	291
20-24	581	8052	180	1.8	131	138	146	155	176	202	216	229	244
25-34	901	13864	199	1.7	144	153	161	172	194	220	239	254	273
35-44	653	9808	217	1.8	153	166	173	187	214	244	260	272	291
45-54	617	9865	227	1.8	160	177	181	198	222	254	271	283	303
55-64	1086	8642	230	2.0	164	178	185	199	225	255	278	289	307
65-74	1045	5576	222	2.0	153	167	175	191	217	250	266	281	301
Black													
20-74	607	6102	208	2.5	133	146	156	171	200	238	260	273	301
20-24	79	1043	171	3.7†	...†	128	134	149	170	193	210	211	...†
25-34	139	1546	199	4.1†	129	136	144	163	192	226	248	259	301
35-44	70	1112	218	8.3†	...†	156	168	176	202	238	275	283	...†
45-54	62	1044	229	7.1†	...†	174	184	195	232	261	268	279	...†
55-64	129	801	223	4.8†	157	168	172	183	218	254	271	299	312
65-74	128	555	217	4.2	149	163	173	183	216	244	261	277	299
Age-adjusted values													
All races, 20-74	...	...	211	1.1	...	...	...	...	...	...	...	...	...
White, 20-74	...	...	211	1.1	...	...	...	...	...	...	...	...	...
Black, 20-74	...	...	209	2.5	...	...	...	...	...	...	...	...	...
Women													
All races†													
20-74	6260	69994	215	1.2	143	156	166	179	210	245	266	282	305
20-24	738	9994	184	1.9	132	140	145	157	180	204	216	230	250
25-34	1170	16856	192	1.4	135	145	154	164	188	215	233	243	263
35-44	844	12284	207	1.8	147	158	164	177	202	231	248	260	276
45-54	763	11918	232	2.2	164	178	188	199	228	257	275	290	306
55-64	1329	10743	249	2.0	180	193	203	215	242	277	299	314	336
65-74	1416	8198	246	1.6	173	189	198	214	241	274	295	309	327
White													
20-74	5416	60785	216	1.3	143	156	166	179	210	248	267	282	305
20-24	624	8408	184	2.1	133	140	147	159	181	204	215	230	249
25-34	1000	14494	192	1.5	135	145	153	164	188	215	235	244	261
35-44	726	10564	207	1.9	147	157	164	177	203	231	248	259	277
45-54	647	10369	232	2.6	166	179	188	199	228	257	274	290	308
55-64	1176	9601	249	1.7	180	193	203	215	244	277	298	312	330
65-74	1245	7329	246	1.7	174	190	199	214	242	275	296	309	328
Black													
20-74	729	7579	212	3.1	140	154	166	176	205	237	263	279	308
20-24	94	1304	185	4.9†	...†	136	144	156	176	204	220	237	...†
25-34	145	1953	191	4.1†	129	144	156	167	190	212	226	235	267
35-44	103	1415	206	4.5†	143	158	170	175	194	233	254	274	279
45-54	100	1215	230	7.2†	150	172	181	200	228	263	277	291	306
55-64	135	959	251	8.0†	178	185	198	211	233	280	318	336	345
65-74	152	733	243	4.2	173	189	198	211	237	269	290	308	323
Age-adjusted values													
All races, 20-74	...	...	215	1.2	...	...	...	...	...	...	...	...	...
White, 20-74	...	...	215	1.2	...	...	...	...	...	...	...	...	...
Black, 20-74	...	...	214	2.7	...	...	...	...	...	...	...	...	...

*Serum cholesterol values are given in milligrams per deciliter. To convert values to millimoles per liter, multiply by 0.02586. From National Center for Health Statistics.[2]

†Includes data for races not shown separately.

Table I-3.—Calculated Levels of Serum Low Density Lipoprotein (LDL) Cholesterol* for Persons 20 to 74 Years of Age Fasting 12 Hours or More, by Sex and Age: Means and Selected Percentiles, United States, 1976-1980

Sex, Age, y	No. of Persons Examined	Estimated Population in Thousands	Mean	SD	Selected Percentiles							
					5th	10th	15th	25th	50th	75th	85th	90th	95th
Men													
20-74	1037	21 262	140	39	80	92	100	113	136	164	181	194	208
20-24	72	1852	109	36	‡	70	74	88	104	129	149	154	‡
25-34	174	5186	128	33	76	87	94	108	128	148	161	171	189
35-44	130	3866	145	40	81	96	105	116	138	176	192	203	206
45-54	106	3543	150	36	99	103	112	119	146	171	189	195	211
55-64	267	3943	148	39	84	101	108	118	147	171	191	206	217
65-74	288	2872	149	40	87	105	109	120	144	174	188	199	217
Women													
20-74	1246	27 102	141	43	81	91	98	110	136	164	186	199	220
20-24	105	3325	114	33	69	74	83	94	106	136	149	155	179
25-34	194	5517	121	33	72	83	90	98	118	139	154	166	187
35-44	166	4800	129	34	78	90	97	107	126	150	163	171	191
45-54	168	5155	157	45	94	104	116	125	156	184	200	213	226
55-64	282	4644	159	42	101	113	118	129	150	188	205	219	237
65-74	331	3661	162	44	98	109	122	135	158	186	207	226	245

*Serum LDL Cholesterol = Serum Total Cholesterol − HDL Cholesterol − (Triglycerides/5). Equation from Friedewald et al.[14] Persons with a serum triglyceride value greater than 400 mg/dL were excluded. From the National Center for Health Statistics: Division of Health Examination Statistics, unpublished data from the second National Health and Nutrition Examination Survey, 1976-1980.
†Includes other races in addition to black and white.
‡Sample size insufficient to produce statistically reliable results.

Table I-4.—Major Causes of Reduced Serum HDL-Cholesterol*

- Cigarette smoking
- Obesity
- Lack of exercise
- Androgenic and related steroids
  - Androgens
  - Progestational agents
  - Anabolic steroids
- β-Adrenergic blocking agents
- Hypertriglyceridemia
- Genetic factors
  - Primary hypoalphalipoproteinemia

Appendix II. Special Patient and Population Groups

This section is provided to review for the practitioner the major forms of severe hypercholesterolemia, the problem of high plasma triglycerides, causes of reduced HDL-cholesterol, and manifestations of diabetic dyslipidemia. Its purpose is to assist the physician in management of these problems or help in identification of disorders that would be better treated by a specialist in this field. There are two reasons for referring a hyperlipidemic patient to a specialist. First, the dyslipidemia may be severe or complicated and beyond the experience of a given practitioner; and, second, the patient may require special testing that is beyond the capability of laboratories available to the physician. The latter may be particularly the case for rare or severe disorders of lipoprotein metabolism. In some instances, a precise etiologic diagnosis may be required for the correct treatment of a patient.

Severe Forms of Hypercholesterolemia

Familial Hypercholesterolemia.—This disorder is caused by a defect in the gene encoding for the LDL receptor such that the receptor is either absent or nonfunctional. One gene for the LDL receptor normally is inherited from each parent. In the heterozygous form of FH, the patient has only one normal gene for LDL receptors, and LDL-cholesterol levels are approximately doubled, to levels exceeding 200 mg/dL. Heterozygous FH occurs approximately once in 500 people, and serum total cholesterol levels usually exceed 300 mg/dL; affected patients frequently have tendon xanthomas, corneal arcus, premature CHD, and a strong family history of hypercholesterolemia. Approximately 5% of patients with myocardial infarction before 60 years of age will have heterozygous FH. Affected men often develop CHD in their 30s or 40s, or even earlier; in women with FH, CHD often occurs in the 50s and 60s. Rarely, about once per million people, individuals inherit two abnormal genes for LDL receptors and hence are homozygous for FH. Their cholesterol levels range from 600 to 1000 mg/dL; they usually have planar and tuberous xanthomas of the hands, elbows, buttocks, and knees, as well as tendon xanthomas. Severe and often fatal coronary disease frequently develops in the teens.

Patients with heterozygous FH rarely respond adequately to dietary therapy alone. Certainly the Step-Two Diet will potentiate the action of specific cholesterol-lowering drugs, and affected patients should be encouraged to modify their diets to obtain maximal cholesterol lowering. Some patients with FH respond remarkably to diet, and the potential value of diet modification should not be overlooked. However, in most patients, it is not necessary to wait for six months of dietary therapy before beginning drug treatment. To obtain the goals of LDL lowering in patients with heterozygous FH, two drugs frequently are required. The combination of a bile acid sequestrant and nicotinic acid is a very potent available regimen. Recent evidence indicates that use of HMG CoA reductase inhibitors (eg, lovastatin) in combination with bile acid sequestrants will reduce LDL-cholesterol levels into the normal range in many people with heterozygous FH. In homozy-

gous FH, more drastic means are required to lower LDL levels. These patients respond poorly to drugs, including reductase inhibitors, and more radical therapies have been tried, including portacaval shunt, liver transplantation, and direct removal of LDL by a modified form of plasmapheresis.

Familial Combined Hyperlipidemia.—Another form of primary hypercholesterolemia occurs in some individual members of families having FCHL. In FCHL, multiple lipoprotein phenotypes can occur in a single affected family. About one third of affected patients have increases in VLDL alone (type 4 hyperlipoproteinemia [HLP] pattern); another third have increases in LDL alone (type 2a HLP), while most others have elevations of VLDL plus LDL (type 2b HLP) or VLDL plus chylomicrons (type 5 HLP). Hyperapobetalipoproteinemia (increased LDL-apolipoprotein B [apo-B] with normal LDL-cholesterol) is another lipoprotein pattern commonly found in FCHL. The diagnosis of FCHL is made by testing of first-degree relatives and by finding multiple lipoprotein phenotypes in a single family. Patients with FCHL are at increased risk for CHD regardless of their lipoprotein phenotype. Familial hypercholesterolemia occurs in about 15% of patients with CHD before 60 years of age. The underlying metabolic defect in many families appears to be an overproduction of lipoproteins by the liver, and the resulting lipoprotein phenotype depends on how rapidly these excess lipoproteins are cleared from the circulation. For example, when rates of clearance of LDL are sluggish, the patient will develop an elevation of LDL-cholesterol.

Dietary therapy can play an important role in the treatment of primary hyperlipidemia due to overproduction of lipoproteins. Patients with FCHL may be extremely sensitive to even a few pounds of excess body weight, and reduction of weight to the desirable range sometimes will lower plasma lipid levels substantially. Further improvement in the lipoprotein pattern may be achieved by instituting a program of regular physical exercise. Restriction of dietary cholesterol and saturated fatty acids may further reduce LDL-cholesterol levels. In many patients with FCHL, however, drug therapy may be required to completely or adequately control plasma levels of lipoproteins. The drug of choice for FCHL is nicotinic acid, which interferes with the excessive formation of lipoproteins. For patients with FCHL who have elevated LDL with normal triglyceride levels and who cannot tolerate nicotinic acid, a bile acid binding resin or the new drug lovastatin can be used; these latter agents alone, however, may not be sufficient in patients with a concomitant elevation of plasma triglycerides, as will be discussed below in the "Hypertriglyceridemia" section.

Severe Primary Hypercholesterolemia.—About 1% of the adult population have cholesterol levels that are persistently over 300 mg/dL. A portion of individuals in this group will have heterozygous FH that is unrecognized, either because of a lack of tendon xanthomas or unavailability of first-degree relatives for testing. In others, a definite monogenic inheritance of elevated LDL-cholesterol cannot be demonstrated, and hence the term "polygenic" hypercholesterolemia has been used. While people in this category may merely represent the upper end of the spectrum of the population distribution of plasma cholesterol, they deserve special attention because of the severity of their hypercholesterolemia and their greatly heightened risk for CHD. Furthermore, patients of this category often have a diet-resistant form of hypercholesterolemia and must be managed with drugs. When it becomes obvious that patients of this type will not reach the goals of LDL lowering by dietary therapy alone, drug treatment can be instituted. Some patients may require a combination of drugs, as described above for FH, but others may respond adequately to a first-choice drug, or the new drug, lovastatin.

Familial Dysbetalipoproteinemia (Type 3 Hyperlipoproteinemia).—This is a relatively uncommon condition that occurs roughly in about one in 5000 persons in the United States, in which catabolism of remnants of VLDL and chylomicrons is delayed. The normal apo-E phenotype is E_3, while the phenotype of type 3 HLP is E_2. The basic abnormality lies in the primary structure of apolipoprotein E (apo-E). The structural alteration of apo-E prevents the normal binding of VLDL remnants to LDL receptors on liver and other cells. The accumulation of modified VLDL remnants (called beta-VLDL) accounts for the term *dysbetalipoproteinemia*. The VLDL in these patients have beta mobility on lipoprotein electrophoresis rather than the normal prebeta mobility. The disorder should be suspected when triglyceride levels are somewhat higher than cholesterol levels in the presence of striking cholesterol elevation. Patients with dysbetalipoproteinemia have an increased risk of premature CHD and peripheral vascular disease; they commonly are obese, glucose intolerant, hyperuricemic, and have tuboeruptive and palmar xanthomas. Despite hypercholesterolemia, the LDL-cholesterol rarely is increased in dysbetalipoproteinemia, and the increase in cholesterol levels occurs in the VLDL fraction; however, when LDL levels are calculated by equation, there will be an apparent increase in LDL-cholesterol. For this reason, in a patient with an elevation in both triglycerides and cholesterol, the physician should be alert to the possibility of dysbetalipoproteinemia, and appropriate testing should be done, including referral to a specialist if necessary.

If a patient with type 3 HLP is overweight, caloric restriction frequently reduces cholesterol levels to normal. If diabetes mellitus contributes to the hyperlipidemia, control of hyperglycemia will often be helpful, but may not eliminate the need to use specific lipid-lowering drugs. Clinical experience has shown that restriction of excess total calories, saturated fatty acids, and cholesterol in the diet will significantly reduce total cholesterol levels in many patients with familial dysbetalipoproteinemia. When hyperlipidemia persists in spite of maximal dietary therapy, drug therapy should be instituted. Nicotinic acid is the drug of choice for this disorder. The fibric acids (gemfibrozil and clofibrate) also have proven highly effective for reducing both cholesterol and triglycerides in dysbetalipoproteinemia. The bile acid sequestrants should not be used as single drug therapy in patients with type 3 HLP because these drugs will increase the cholesterol and triglyceride levels.

Hypertriglyceridemia

Definition.—The National Institutes of Health (NIH) Consensus Development Conference on Treatment of Hypertriglyceridemia defined definite hypertriglyceridemia as a fasting plasma triglyceride level exceeding 500 mg/dL.[8] This conference classified triglyceride levels in the range of 250 to 500 mg/dL as "borderline hypertriglyceridemia." The NIH Consensus Panel concluded: "There is little evidence that triglyceride levels below 250 mg/dL in the presence of normal cholesterol levels predict an increased risk of any disease. These levels (generally) can be considered normal." The present report generally follows the recommendations of this NIH Consensus Panel.

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For most patients, triglyceride levels in the range of 250 to 750 mg/dL result mainly from increases in VLDL (type 4 HLP). When triglyceride levels are higher, the patient usually has elevations of both VLDL and chylomicrons (type 5 HLP). Very rarely patients have a congenital absence of lipoprotein lipase and have severe chylomicronemia (type 1 HLP).

Plasma Triglycerides and Disease.—The relationship between plasma triglyceride levels and cardiovascular disease is controversial. Although plasma triglyceride levels are positively associated with increased risk for cardiovascular disease in most population studies, in most they were not independently predictive for CHD after statistical adjustment for closely associated attributes such as total cholesterol, HDL-cholesterol, hypertension, cigarette smoking, and obesity. In the Framingham Heart Study, however, the plasma triglyceride level was found to be an independent predictor of CHD in women.[41] Even so, the plasma triglyceride level, rather than being a direct cause of atherosclerotic disease, probably reflects the presence of certain atherogenic lipoproteins. Certainly, many disease entities that elevate triglyceride levels, such as diabetes mellitus, nephrotic syndrome, and chronic renal disease, carry an increase in risk for CHD. Furthermore, some patients with FCHL have borderline hypertriglyceridemia and normal serum cholesterol levels and yet are still at increased risk for CHD. In these situations, the high triglyceride level may be a clue to the presence of other lipoprotein abnormalities that are more directly associated with CHD, such as low HDL-cholesterol, low apoprotein A-1, elevated apoprotein B, or atherogenic remnant lipoproteins that have not been well defined. When assessing the risk for CHD in a patient with borderline hypertriglyceridemia, reliance should be placed first on the standard cholesterol risk factors, viz, total cholesterol, LDL-cholesterol, and HDL-cholesterol. Beyond these, additional factors suggesting increased coronary risk in patients with hypertriglyceridemia are the presence in first-degree relatives of hypercholesterolemia, premature CHD, and, if the test is available, increased plasma levels of apo-B.

A link between plasma triglycerides and disease is most clearly evident in patients who have severe hypertriglyceridemia with chylomicronemia and eruptive xanthomata; these patients are prone to abdominal pain and/or pancreatitis, the latter occasionally being fatal. Severe elevations of chylomicrons directly induce pancreatitis, which can be prevented by triglyceride reduction.

Candidates for Specific Therapy.—Much of *borderline hypertriglyceridemia* seen in clinical practice is due to various exogenous or secondary factors raising the plasma triglyceride level. The most common is obesity. Others include excessive intake of alcohol, diabetes mellitus, hypothyroidism, chronic renal disease—uremia, nephrotic syndrome, maintenance dialysis, renal transplantation—liver disease, and, rarely, dysproteinemias. There are also a number of drugs that raise lipid levels as a significant side effect. These may primarily act on VLDL and raise triglyceride levels, rather than act on LDL. These include several drugs used to lower blood pressure (including the thiazide diuretics and β-adrenergic blocking agents), estrogenic hormones (including oral contraceptives), and retinoids. The clinician evaluating a patient's blood lipid levels should be aware of this phenomenon.

Borderline hypertriglyceridemia also can be one manifestation of certain familial hyperlipidemias. One such entity is FCHL, described above. Patients with FCHL have an increased risk for CHD regardless of their lipoprotein phenotype, including isolated borderline elevated plasma triglycerides. Because of heightened coronary risk, patients with FCHL deserve treatment with diet first, and, if necessary, with drugs. Furthermore, any patient with primary borderline hypertriglyceridemia who already has clinical manifestations of premature cardiovascular disease can be treated as if he or she has FCHL.

Borderline hypertriglyceridemia likewise can be a manifestation of another familial disorder called familial hypertriglyceridemia (FHTG). Most patients with FHTG appear to have a mild defect in lipolysis of triglyceride-rich lipoproteins combined with an overproduction of VLDL triglycerides. The VLDL are enriched in triglycerides, but the number of VLDL particles entering plasma apparently is not increased, and consequently LDL-cholesterol concentrations are not increased. Patients with FHTG seem to be at lesser risk for CHD than those with FCHL. In FHTG, there generally is a lack of elevated blood cholesterol, either in the patient or other family members, and affected members are less likely to have premature CHD. Caloric restriction and increased exercise can be strongly recommended for obese patients with FHTG, but drug therapy is generally not appropriate for this condition alone.

The NIH Consensus Panel based its definition of *definite hypertriglyceridemia* on the following considerations: "Fasting plasma triglyceride levels above 1,000 mg/dL carry a significant risk of pancreatitis. Based on this risk coupled with the large intraindividual variation in repeated triglyceride measurements, a triglyceride level greater than 500 mg/dL is considered to be abnormal, and warrants the label hypertriglyceridemia." Patients with definite hypertriglyceridemia also can have primary or secondary disorders of triglyceride metabolism, and, not infrequently, these two categories are present in a single patient.

Very high triglyceride levels (>1000 mg/dL) are due in large part to accumulation of chylomicrons. Rare genetic causes of severe chylomicronemia are congenital absence of lipoprotein lipase or apolipoprotein C-II, the latter being required for activation of lipoprotein lipase; these conditions usually become manifest first in childhood. Severe hypertriglyceridemia in adults sometimes is due to a primary disease (FHTG or FCHL) plus exacerbating secondary factors such as obesity, poorly controlled diabetes mellitus, excess use of alcohol, or drugs (eg, corticosteroids, estrogens, or β-adrenergic blocking agents). In such patients, both children and adults, immediate and long-term reduction of plasma triglycerides is mandatory to prevent recurrent abdominal pain and pancreatitis.

Dietary Therapy in Patients With Hypertriglyceridemia.—Changes in life-style (control of weight, increased physical activity, restriction of alcohol, and, in some cases, restriction of dietary fat) are the primary modes of therapy for hypertriglyceridemia. Patients with triglyceride levels in excess of 500 mg/dL, like those with high cholesterol levels, may benefit from counseling with a registered dietitian. Specific dietary approaches to the major forms of hypertriglyceridemia can be considered briefly.

For patients with severe hypertriglyceridemia and chylomicronemia, a very-low-fat diet (10% to 20% of total caloric intake as fat) should be instituted to prevent pancreatitis. The need to maintain this diet at all times must be emphasized. Some chylomicronemic patients are extremely sensitive to dietary fat and can develop pancreatitis from a single high-fat meal. In some patients, repeated bouts of pancreatitis will occur despite all attempts at dietary control, and drug therapy will be required.

In patients with borderline hypertriglyceridemia, emphasis should be on weight reduction and increasing physical activity. In this condition, very-low-fat, high-carbohydrate diets are not required and may actually accentuate hypertriglyceridemia. Therefore, it is not advisable to go beyond the Step-One Diet in reduction of fat intake. With secondary hypertriglyceridemias, one should treat the underlying disorder, but sometimes treatment can be facilitated by modifying the diet, usually by weight reduction and alcohol restriction.

Drug Therapy in Patients With Hypertriglyceridemia.—The NIH Consensus Panel reported: "drug therapy in hypertriglyceridemia should take a second place to modification of the diet. Drugs nevertheless may be required to avoid abdominal pain and pancreatitis in the presence of chylomicronemia. They also can be used to produce regression of xanthomata in patients of this kind or in those with familial dysbetalipoproteinemia. Drugs also may be employed in the attempt to retard atherogenesis in patients with genetic hyperlipidemias, such as FCHL or familial dysbetalipoproteinemia." The current report supports these recommendations.

For patients with marked hypertriglyceridemia, who do not respond adequately to modification of the diet, drug therapy can be justified to reduce the risk for acute pancreatitis. Nicotinic acid is the drug of choice here, but if this drug is not tolerated, many patients will respond sufficiently to a fibric acid (gemfibrozil or clofibrate) to eliminate the risk for pancreatitis. Bile acid binding resins are not appropriate for patients with hypertriglyceridemia.

The role of drugs in the treatment of borderline hypertriglyceridemia is controversial. Most patients in this category will have diet-induced hypertriglyceridemia and thus are not candidates for drug therapy. If a patient has the characteristics of FHTG, which does not carry an increased risk of CHD, the use of drugs is not warranted. On the other hand, if a hypertriglyceridemic patient has been shown to have FCHL, which imparts increased risk, lipid-lowering drug therapy is appropriate. Nicotinic acid is the drug of choice for FCHL, because it curtails the overproduction of lipoproteins that is characteristic of this disorder. An alternative approach is to reduce triglyceride levels with a fibric acid and to simultaneously lower LDL concentrations with either a bile acid binding resin or lovastatin. If a diagnosis of FCHL cannot be made by family testing, factors that suggest the presence of this disorder in individual patients include the presence of CHD, high blood cholesterol, high-risk LDL-cholesterol, reduced HDL-cholesterol, and a family history of CHD. Opinion is divided whether such patients are candidates for drug therapy. A conservative approach is to restrict the use of drugs to patients with high levels of total cholesterol and LDL-cholesterol. A more aggressive approach is to treat elevated triglycerides, high VLDL-cholesterol levels, and reduced HDL-cholesterol concentrations with nicotinic acid or a fibric acid; however, it must be emphasized that this latter approach has not been proven by controlled clinical trials to reduce the risk for CHD.

Reduced HDL-Cholesterol

In this document, a reduced serum level of HDL-cholesterol is defined as a concentration below 35 mg/dL. A reduced HDL-cholesterol level imparts an increased risk for CHD, and hence is classified as a major risk factor. As indicated in the text, the HDL-cholesterol concentration should be measured in all patients with high blood cholesterol levels, and in persons with borderline-high blood cholesterol levels and a high risk status (definite CHD or two other major risk factors, one of which can be male sex). The presence of a reduced serum HDL-cholesterol is one factor favoring the use of drugs to treat high LDL-cholesterol concentrations.

The major causes of a reduced serum HDL-cholesterol level are listed in Appendix I, Table 4. Heavy cigarette smoking is a documented cause, and, in smokers, the reduction in HDL-cholesterol appears to be made worse by concomitant heavy use of coffee. Obesity is a major cause of reduced concentrations of HDL, and a closely related cause is a lack of physical activity. White men, but not necessarily black men, have lower HDL levels than women. Anabolic steroids and progestational agents decrease the HDL-cholesterol concentration. Among other drugs, the β-adrenergic blocking agents most consistently reduce the HDL level. Hypertriglyceridemia, even in mild forms, is frequently associated with significantly decreased levels of HDL-cholesterol, and, in some patients, elevated LDL-cholesterol is accompanied by a reduced concentration of HDL. Finally, poorly understood genetic factors account for a portion of cases of reduced HDL-cholesterol.

Although there have been no clinical trials demonstrating that the benefit of raising HDL-cholesterol, the connection between reduced HDL-cholesterol and CHD risk justifies the attempt to raise HDL levels, particularly when this can be accomplished by hygienic means. Appropriate advice is to stop use of cigarettes in smokers, reduce body weight in the obese, increase exercise in the sedentary, and avoid use of anabolic steroids in athletes. For patients with a reduced HDL-cholesterol, avoiding the use of beta-blockers for treatment of hypertension may be prudent, although these drugs may be required for patients with definite CHD. One result of treating hyperlipidemia is that HDL-cholesterol concentrations frequently increase, which may be of added benefit.

Diabetic Dyslipidemia

Diabetes mellitus is a major risk factor for CHD, and, in accord with the recommendations of this report, the minimal goal of LDL lowering in diabetic men is to achieve a reduction of LDL-cholesterol to less than 130 mg/dL. For diabetic women, the minimal LDL-cholesterol goal is <160 mg/dL in the absence of CHD or another risk factor, or <130 mg/dL if definite CHD or another risk factor is present. Abnormal plasma lipid and lipoprotein levels frequently are seen in diabetics. Careful control of plasma glucose will reduce LDL levels, and HDL-cholesterol concentrations frequently will rise. Control of hyperglycemia is the key to improving the lipoprotein pattern in diabetics. The dietary therapy outlined for other high-risk patients with elevated LDL levels is recommended by many authorities for diabetic patients. Other investigators believe that intake of carbohydrates should not exceed 40% to 45% of total calories; if this latter approach is accepted, the intake of saturated fatty acids and cholesterol still should be curtailed, as recommended for other patients at high risk.

The most obvious lipoprotein abnormality in patients with noninsulin-dependent diabetes mellitus (NIDDM) is hypertriglyceridemia. In occasional, poorly controlled diabetics, severe chylomicronemia can develop, and risk for acute pancreatitis is high. In these unusual patients, intake of fat must be severely restricted, at least temporarily, to prevent further synthesis of chylomicrons; furthermore, adequate doses of insulin are needed to restore normal activity of lipoprotein lipase. The milder forms of hypertriglyceridemia that occur in many diabetics are the result of poor control of hyperglycemia, and their triglycerides

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can be reduced by improved glucose control. If hypertriglyceridemia persists despite good control of plasma glucose levels, the patient may have an underlying familial form of hyperlipidemia.

Pregnant Women With Preexisting Lipid Disorders

Generally, the dietary therapy previously prescribed for the lipid disorder should be continued during pregnancy. If dietary therapy is very restrictive, careful consideration should be given to assuring adequate nutrient intake. Drug therapy should be discontinued during pregnancy, since the effect of lipid-lowering drugs on the fetus has not been carefully studied. Women with a prior history of hypertriglyceridemia should be monitored carefully; triglyceride levels above 1000 mg/dL are associated with an increased risk of pancreatitis. Consultation with a lipid specialist may be indicated for patients with severe forms of hyperlipidemia.

Appendix III. Intensive Dietary Instruction and Behavior Modification

In a majority of patients with high-risk LDL-cholesterol levels, the Step-One Diet should prove sufficient to reach the goals of dietary therapy. For most patients, it should not be necessary to refer to a dietitian. A dietitian can, however, be helpful even for these patients. For a minority of patients, more intensive dietary therapy will be needed, and referral to a registered dietitian will be important in order to effectively implement therapy. The dietitian can play a vital role in education of the patient in the process of dietary change, and the dietitian will be especially valuable for instruction of the patient in the Step-Two Diet. In this Appendix, the general approach to intensive dietary therapy under the supervision of a registered dietitian is outlined. The purpose of this section is to provide the physician and immediate staff with information about the techniques employed by many dietitians for institution and maintenance of intensive dietary therapy (including the Step-Two Diet). If the physician and staff are thoroughly familiar with the principles of dietary therapy, as outlined in this Appendix, this understanding will facilitate their interaction with the dietitian and will increase the chances of success in achieving the goal of therapy by diet modification alone. The usual steps employed by the dietitian are the following.

Assessment of Nutritional Status and Eating Habits.—A thorough assessment of the patient's dietary history and current eating habits is useful in implementation of dietary change. This assessment will include the recording of the patient's current weight and weights at significant ages. The dietitian will estimate percentage of desirable body weight, and, in some cases, the percentage of body fat, to determine whether the patient needs to lose weight. A detailed description of current eating habits will be obtained. Examples of the types of information that are obtained include the following: (1) What times of the day does the patient usually eat? (2) Are some meals routinely skipped? (3) At what time does the patient eat his/her largest meal? (4) Where are meals typically prepared (eg, in a restaurant, work cafeteria, fast-food restaurant, deli, at home, or in the homes of others)? (5) Are meals eaten at home prepared from packaged foods or fresh from the market? (6) Which are favorite foods and what foods are disliked? and (7) What foods will be most difficult to increase or decrease? Furthermore, the dietitian will attempt to assess the patient's general state of knowledge of nutrition and its relation to high cholesterol levels, educational level, motivation, attitudes toward diet, and structure of social support.

Initial Instructions for Diet Modification.—The dietitian will describe for the patient an overall plan for diet modification. The connection between dietary habits and blood cholesterol level will be emphasized, and particular emphasis will be given to reducing the consumption of saturated fatty acids and cholesterol, and to reducing excess body weight. The dietitian may review the contents of Table 7 with the patient and will give particular attention to foods that are unusually rich in saturated fatty acids and cholesterol. A few individuals may be taught to compute a daily record of food intake that delineates specific foods, where they are prepared, and their quantity. To learn to record quantities of different foods will require specific instruction for using measuring cups, spoons, and a food scale. The dietitian may feel that certain patients will benefit by keeping a food record for about three days as an educational exercise.

In this initial instructional process, the dietitian likely will review the patient's daily routine both during the week and on weekends, and will assist the patient in identifying life-style factors that might interfere with adherence. The patient will be urged to actively participate in discussion and may be given the option of evaluating several eating plans before deciding on a final diet plan. It will be pointed out to the patient that he/she may find certain foods to be unappealing at first, but over a period of time, new preferences in taste will develop.

Particular attention will be given to the sources of fat in the diet, especially fat that is "hidden" in foods such as bakery goods, cheeses, and processed meats. Suggestions will be made on how to select appropriate snack foods and prepared foods. The patient may be taught the principle of "controlled cheating," ie, how to plan and adjust for occasional episodes off the diet without becoming discouraged and discontinuing the diet altogether. Instruction will be given on how to change the type of milk used, how to reduce meat portion size, how to substitute egg whites for whole eggs in baking, and how to use margarines and oils in the place of fats rich in saturated fatty acids. The dietitian probably will attempt to involve other individuals of significance (eg, parents, spouse, and children) in dietary instructions.

Institution of Fat-Modified Diets.—Patients usually are started on a diet that corresponds as closely as possible to their normal eating habits. For example, if the patient always skips breakfast, he/she will not be requested to eat breakfast at the outset. If the patient always eats lunch in the cafeteria at work, he/she will be taught to make reasonable food choices rather than starting to bring lunch from home. Specific goals for eating habits will be set to allow progress toward the attainment of the composition of the Step-One Diet. Only after this first step has been attained will the dietitian attempt to progress to the Step-Two Diet.

Although the objective of the Step-One Diet is less than 10% of calories as saturated fatty acids, it usually is difficult for the average person to estimate whether the target is being met. A realistic approach will provide specific recommendations about diet change, such as reducing meat portion size to four ounces, or substituting a tuna sandwich for a cheese sandwich two days a week. It usually is necessary to implement the specific goals in a graduated fashion, rather than all at once. This will prevent the patient from being overwhelmed, will allow him/her sufficient time for adjustment, and will engender a feeling of success and not failure. Some patients will be asked to self-monitor eating behaviors related to their eating-habit goals on a regular basis during the initiation phase. The

dietitian may need to review these records periodically to detect problem areas. Finally, a schedule for follow-up visits with the dietitian often is employed to ensure adoption of and adherence to the new diet.

Strategy for Behavior Modification.—Involvement of the patient in developing appropriate behavior strategies is crucial for successful dietary change and long-term adherence to the recommended diet. For the obese patient, techniques of behavior modification have been moderately successful for achieving weight reduction, and they may be instituted for overweight patients. Further, the dietitian may modify these techniques to train patients to alter the diet composition. These techniques focus on unconscious eating habits, compulsive behavior, binge eating, lack of resistance to social pressures for eating cholesterol-raising foods, use of eating to relieve anxiety and depression, and lack of will power or self-control. The dietitian can explore all of these areas with the patient and guide him/her in overcoming these eating problems. Patients will be given the opportunity to "talk through" their eating problems and to "brainstorm" new ways to improve their eating behavior.

Monitoring and Reinforcement.—Progress in achieving the specified dietary goals will be monitored by both the patient and the diet counselor. It is helpful for the physician to provide information on response in cholesterol levels as a guide to success in diet modification. Self-monitoring tools that are designed to meet the needs of the patient may be utilized. For example, three-day food records often are an effective monitoring tool. These records provide an estimate of adherence and can help to identify any real or potential problems. These records also can enable the patient to become more aware of the diet and related behaviors, assist in analysis of progress in dietary change, and provide reinforcement of new behavior.

A schedule of regular follow-up visits is helpful to achieve adherence to the diet. There is a tendency for adherence to drift downward with time, and this often can be avoided by periodic visits with the dietitian. It will be especially important to give supportive followup and assistance during periods of life change or stress (eg, marriage or divorce, loss of loved ones, job change); renewed self-monitoring during these periods may be especially helpful. Occasional meetings with other family members can help to reinforce adherence to diet modification. A constant review of the basics will be needed to offset distortions of information resulting from misunderstandings or erroneous messages picked up from the media or other sources.

Individuals are increasingly making use of personal computers for activities at home. Software programs are now available, or will become available, for analyzing food records, for providing nutrient analysis, and for support of changes in eating patterns. These programs are available for both the lay public and for professionals at several levels of complexity. Their use for modification of the diet for individuals seems to hold great potential.

Role of the Patient and Family in Dietary Therapy.—Although intakes of saturated fatty acids and cholesterol have declined in the United States, most of our population continues to consume a diet that contributes to undesirably high cholesterol levels. The current social environment often does not provide easy access to appropriate food choices nor does it sufficiently reinforce diet modification. It is thus helpful to incorporate a social support element in nutrition education and dietary counseling. Inclusion of family and spouses in intervention sessions will significantly increase the chances of success of dietary strategies to lower cholesterol. Worksite and group strategies may be particularly successful when they integrate dietary change into the social context. New interactive methods have advantages over traditional didactic methods for providing information and reinforcement.

Appendix IV. Practical Suggestions to Improve Drug Adherence

Pre-Initiation Assessment.—In addition to selection of a drug based on its efficacy, an attempt should be made to select a drug that the patient is likely to tolerate. The patient should participate in this discussion and can be given the option of evaluating several drugs before deciding upon the final treatment plan. A few examples of the type of preliminary deliberation might include the following:

Sequestrants.—Good choice for young, motivated, and safety-conscious individuals. May not be a good choice for the patient who has significant constipation, existing hemorrhoids, recurrent symptoms of peptic ulcer or hiatus hernia; has a history of taking multiple drugs; or travels extensively.

Nicotinic Acid.—Good choice where cost is a major consideration, a tablet is preferred, or long-term effects on CHD or safety are desired. The drug may not be tolerated in the postmenopausal woman with flushing, or in the patient with angina pectoris or extensive coronary disease.

Lovastatin.—Good choice for the patient receiving multiple medications, with extensive disease, or severe forms of hypercholesteremia. The patient may have concerns about the lack of long-term safety information.

There are no absolute predictors of adherence, but one should be prepared to offer special assistance to patients with conditions frequently associated with reduced adherence. These include the following: current life changes, eg, marital status change, job or housing change, and so on; current or past history of psychological distress; smokers; lack of social support; erratic or irregular schedules; and recurring physiological complaints, particularly those that might be exacerbated by any side effects of the medication.

Pre-Initiation Education (This Is Particularly Important With the Bile Acid Sequestrants and Nicotinic Acid).—*Sequestrants.*—Demonstrate preparation of medication. Discuss how volume of fluid may affect palatability and large volumes may increase the sense of fullness. Rapid ingestion may cause air swallowing. If water is unsatisfactory, an unsweetened juice (avoid calories) may improve palatability. A heavy or pulpy juice may minimize complaints relative to consistency. Fluid and fiber intake (the latter may also produce some additional cholesterol lowering effect) should be increased to alleviate constipation. Laxatives should not be used, but stool softeners may be indicated occasionally.

Nicotinic acid.—Discuss flushing, its expected duration, development of tolerance, and the need to avoid taking medication on an empty stomach. Flushing may be diminished initially by pretreatment with an inhibitor of prostaglandin synthesis or use of a variety of sustained-release preparations such as Nico-Bid. Note that the cost of the sustained-release preparations is much greater than that of the usual nicotinic acid tablets.

Identify the most likely side effects and ways the patient has handled such symptoms in the past. Identify ways the patient can manage these side effects should they occur. It is important to reinforce the patient's capability to manage these symptoms if they do occur.

Review the patient's daily routine both during the week and on weekends. Help the patient to identify life-style factors that might interfere with adherence, and to identify

ways in which the regimen or the daily routine could be adjusted to enhance adherence.

Teach the patient how to maintain a daily record of medication intake as well as how to use that record to identify factors, if any, which contribute to missed medication doses or to self-adjustments to the medication dosage.

Teach the patient about cholesterol-adherence relationships. In particular, stress the variability that exists in measured cholesterol values due to both laboratory and biological factors (eg, measurement methods, laboratory variation, seasonal variability, weight change, dietary intake, and stress).

Initiation of Treatment.—Tailor drug regimen to patient characteristics rather than asking for life-style changes in addition to those already prescribed.

Establish a regular follow-up schedule that will allow for the early identification and remediation of any problems. If possible, supplement the regular visit schedule with between-visit telephone checks until the regimen is solidly in place.

Gradually build up to the prescribed dose to minimize the occurrence of side effects and to allow the patient to adjust to the regimen.

Introduce self-monitoring and review these records at follow-up appointments until the patient is consistently adhering to the medication regimen at full dosage. Assist with any adherence difficulties promptly.

Ongoing Maintenance of Adherence.—Provide regular feedback to the patient regarding his or her cholesterol level so that the patient is aware of the treatment's success, and thus, the importance of adherence.

Involve spouses or other family members in the patient's therapy. Social support has a strong influence on long-term adherence.

Request that the patient periodically self-monitor adherence to the medication regimen. Use these records to evaluate the patient's adherence and to identify any difficulties the patient may be experiencing.

Maintain regularly scheduled followup with the patient, with active pursuit after missed appointments. Regular supervision is an important factor in maintaining adherence.

Give prompt attention to any changes in treatment response or in adherence.

Increase attention and the frequency of follow-up visits or telephone contact during periods of life stress or life change to minimize the adherence problems that are likely to ensue.

Encourage self-monitoring during periods of stress or life change to help the patient maintain awareness of the medication regimen and to identify problems that may be arising.

Teach the patient to solve problems. The ability to manage everyday therapy problems helps remove barriers to effective treatment.

Exhibit 2

The ingredients were compounded together to form a tablet. Two study groups consisting of eleven and fourteen patients each were formed. Blood samples were taken from the patients, and tested for total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol to establish baseline levels from which fluctuations in these lipids could be compared. The patients were then placed upon a regimen of the above discussed tablets, totaling approximately 1500 mg of nicotinic acid, once per day before going to bed. After eight weeks of this regimen, the patients were again tested for lipid profiles. The results of the tests conducted at eight weeks, showing the changes in the lipid profiles as a percentage change from the baseline, are reported in the table hereinbelow. Positive numbers reflect percentage increases and negative numbers reflect percentage decreases in this table.

AMENDED

TABLE II

Patient Study Lipid Profile Data

GROUP A

Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL_2-C	Lp(a)
1	-11.9	-17.9	NA	-17.3	22.0	NA	NA
2	-9.4	-33.1	NA	-28.7	65.4	NA	NA
3	-20.6	-13.1	NA	-43.7	-6.3	NA	NA
4	-7	-15.9	NA	61.6	3.8	NA	NA
5	-20.3	-24.3	NA	-28.8	11.1	NA	NA
6	-15.6	-31.2	NA	-42.0	51.6	NA	NA
7	-27.6	-36.8	NA	-39.4	12.5	NA	NA
8	-10.6	-13.8	NA	-42.4	18.8	NA	NA
9	4.5	1.1	NA	7.2	9.2	NA	NA
10	-.7	-5.5	NA	-2.7	22.9	NA	NA
11	-15.4	-.4	NA	-67.6	50.0	NA	NA
Mean	-12.3	-17.4	NA	–22.1	23.7	NA	NA
p-Value	0.0004	0.0001		0.0371	0.0068		

GROUP B

Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL_2-C	Lp(a)
1	-19.2	-27.1	-24.4	-33.4	20.0	22.3	8.1
2	-32.2	-35.7	-28.0	-60.4	4.3	3.2	-25.3
3	-17.3	-28.4	-35.6	-41.6	34.6	38.6	0
4	-19.9	-24.6	-15.1	-20.8	9.6	16.1	-27.0
5	-3.3	-2.1	-29.4	-41.1	5.8	-2.3	-22.4
6	PATIENT WITHDREW FROM STUDY						
7	-23.1	-32.6	-40.8	-58.6	49.2	62.1	-14.3
8	24.8	34.0	-28.4	5.5	6.5	0	NA
9	10.1	12.0	-16.8	-11.6	20.7	-11.6	40.6
10	-2.9	-7.7	-28.0	-59.0	53.1	70.5	-41.2
11	-10.5	-18.8	-31.3	-53.4	31.8	34.2	NA
12	-20.0	-30.8	-30.4	11.7	21.1	25.0	-28.4
13	-9.4	-16.6	-17.5	-46.9	52.3	51.9	-17.6
14	17.4	16.8	-22.6	-17.5	51.3	5.4	38.5
Mean	-8.1	-12.4	- 26.8	- -32.9	27.7	24.3	-6.9
p-Value	0.0002	<0.0001	0.0001	<0.001	<0.0001	0.0002	<0.0188
Combine	-8.7	13.3	Gp B	-26.1	25.3	Gp B	Gp B
p-Value	0.0002	<0.0001	only	<0.0001	<0.0001	only	only

The data reported in TABLE II shows that the LDL levels in the Group A patients had a mean decrease of –17.4% and triglyceride decrease of –22.1%. HDL cholesterol levels, the beneficial cholesterol, were raised by 23.7 in this Group. Similar results were

obtained with the Group B patients. These studies demonstrate that dosing the sustained release formulation during the evening hours or at night provides reductions in LDL cholesterol levels equal to immediate release niacin on a milligram per milligram basis, but superior reductions in triglyceride reductions when compared to sustained release formulation dose during daytime hours on a milligram per milligram basis. Additionally, the increases in HDL cholesterol obtained from dosing the sustained release formulation during the evening or at night were +23.7% for one group and + 27.7% for the other group. Dosing during the evening therefore provides reduction in LDL cholesterol plus significant decreases in triglycerides and increased in HDL cholesterol with once-a-day dosing.

Groups A and B were also tested for liver enzymes (AST, ALT and Alkaline Phosphatase), uric acid and fasting glucose levels at the start of the study described hereinabove (to form a baseline) and at two, four and eight week intervals. The results of these tests are listed in TABLES III-VII hereinbelow.

Exhibit 3

TOTAL CHOLESTEROL
NIASPAN GROUP

PATIENT NUMBER	DATE STOPPED	BASELINE mg/dL	After Treatment mg/dL	% Change
5	9/10/90	290.3	263	-9.4
7	9/28/90	284.0	231	-18.7
11	11/12/90	262.3	208	-20.3
15	12/6/90	311.7	263	-15.6
18	12/21/90	293.0	212	-27.6
22	12/27/90	258.3	231	-10.6
26	12/28/90	291.0	289	-0.7
Mean		284.4	242.6	-14.7
Std Dev		18.6	29.8	8.7
p-value			0.005	

ACCT NO. 20411

Clinical Laboratories

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PAGE 1

SS FLORIDA, INC.
8244 S. MILITARY TRAIL S-190
...Y BEACH, FL 33484

LAB NO. 0289761
DATE COLLECTED 06/27/90
TIME COLLECTED 0950
DATE ENTERED 06/27/90
DATE REPORTED 06/28/90 5131AM
REPORT STATUS FINAL

AGE 52 SEX F

0627901237807368059F

** CONFIDENTIAL REPORT **
SA 60 ROUTE WS STOP 160
MMENTS:

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
ENZYME PLUS/CBC/DA					
ENZYME					141
GLUCOSE	101		MG/DL	80 - 125	
SODIUM	140		MEQ/L	135-148	
POTASSIUM	4.6		MEQ/L	3.3-5.3	
CHLORIDE	106		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	24		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	10			5-15	
UREA NITROGEN	20		MG/DL	7-25	
CREATININE	1.0		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	20			8-20	
URIC ACID	4.0		MG/DL	2.5 - 7.5	
CALCIUM	10.1		MG/DL	8.5-10.5	
PHOSPHORUS, INORGANIC	3.4		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.9		GM/DL	6.0-8.5	
ALBUMIN	4.2		GM/DL	3.2-5.5	
GLOBULIN	2.7		GM/DL	1.5-3.8	
A/G RATIO	1.6			1.1-2.2	
CALCIUM, IONIZED	4.5		MG/DL	3.6-4.8	
BILIRUBIN, TOTAL	0.3		MG/DL	0.2-1.2	
[redacted]					
TOTAL	103		U/L	20 - 140	
LACTATE DEHYDROGENASE	130			80-250	
ASPARTATE TRANSAMINASE					
(SGOT)	24		U/L	0-40	
ALANINE AMINOTRANSFERASE					
(SGPT)	20		U/L	0-40	
CHOLESTEROL, TOTAL	[redacted]		MG/DL	0 - 199	
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES	94		MG/DL	20-190	
[redacted]					
CBC WITH DIFFERENTIAL					
WHITE BLOOD CELLS	4.4		THOUSAND/CU.MM.	3.8 - 10.8	
RED BLOOD CELLS					
HEMOGLOBIN (B)	13.9		GM/DL	12.0 - 15.6	
HEMATOCRIT					
HCV	41.4		PERCENTILES	80.0 - 100.0	
MCH	30.3		MICROGRAMS		
MCHC	33.7		%	32.0 - 36.0	
RDW	14.1		PERCENT		
PLATELET COUNT	204		THOUSAND/CU.MM.	130 - 400	
NEUTROPHILS	56			40 - 75	
NEUTROPHILS, ABSOLUTE	2.47		THOUSAND/CU.MM.	1.50 - 8.10	

** REPORT CONTINUED ON NEXT PAGE **

N/2

INDICATES TESTING SITE SEE REVERSE SIDE †

ACCT. NO. 25433

JD Clinical Laboratories

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PAGE 1

65 FLORIDA INC
6244 S. MILITARY TRAIL S 590
DEERFIELD BEACH, FL 33484

LAB NO. 0209326
DATE COLLECTED 07/02/90
TIME COLLECTED 0830
DATE ENTERED 07/02/90
DATE REPORTED 07/06/90 5:29AM
REPORT STATUS FINAL

AGE 52 SEX F

* CONFIDENTIAL REPORT **

IEA 90 ROUTE MS STOP 160

IMMENTS: FASTING

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
ENZYME PROG/CIRC/UA					
CHEMZYME					
GLUCOSE	100		MG/DL	80 - 125	
SODIUM	143		MEQ/L	135 - 148	
POTASSIUM	4.2		MEQ/L	3.5 - 5.3	
CHLORIDE	106		MEQ/L	95 - 110	
CARBON DIOXIDE CONTENT	23 L	NCS	MEQ/L	24 - 32	
ELECTROLYTE BALANCE	15			5 - 15	
UREA NITROGEN	11		MG/DL	7 - 25	
CREATININE	0.9		MG/DL	0.6 - 1.4	
BUN/CREATININE RATIO	12 L	NCS		8 - 20	
URIC ACID	4.3		MG/DL	2.5 - 7.0	
CALCIUM	9.5		MG/DL	8.5 - 10.6	
PHOSPHORUS, INORGANIC	3.7		MG/DL	2.5 - 4.5	
PROTEIN, TOTAL	6.6		GM/DL	6.0 - 8.3	
ALBUMIN	4.3		GM/DL	3.5 - 5.0	
GLOBULIN	2.3		GM/DL	1.5 - 3.8	
A/G RATIO	1.9			1.1 - 2.2	
CHOLESTEROL, TOTAL	143		MG/DL	140 - 200	
BILIRUBIN, TOTAL	0.3		MG/DL	0.2 - 1.2	
ALKALINE PHOSPHATASE, TOTAL	86		U/L	20 - 140	
LACTATE DEHYDROGENASE	130		U/L	0 - 250	
ASPARTATE TRANSAMINASE (SGOT)	22		U/L	0 - 50	
ALANINE AMINOTRANSFERASE (SGPT)	25		U/L	0 - 50	
[redacted] TOTAL			MG/DL	0 - 190	
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES	97		MG/DL	20 - 190	
IRON, TOTAL			MCG/DL	50 - 170	
CBC, PLATELET, & DIFF					
NO SPECIMEN RECEIVED					
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	70		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 40					
FEMALE GREATER THAN 50					
HDL CHOLESTEROL	100 H		MG/DL	LESS THAN 130	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE

SD Clinical Laboratories

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ACCT. NO. 25411

ES-FLORIDA INC
6244 S MILITARY TRAIL S-590
...Y BEACH, FL 33484

** CONFIDENTIAL REPORT **
EA 00 ROUTE W3 STOP 160
MMENTS: NONFASTING

LAB NO. 2502783
DATE COLLECTED 09/07/90
TIME COLLECTED 9.15A
DATE ENTERED 09/07/90 05
DATE REPORTED 09/08/90 9:03AM
REPORT STATUS FINAL
0907901234O7652679F

[redacted]
PAGE
AGE 53 SEX F

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
HEMZYME PLUS/CBC/UA					
CHEMZYME					MI
GLUCOSE	101		MG/DL	80 - 125	
SODIUM	140		MEQ/L	135-148	
POTASSIUM	4.4		MEQ/L	3.5-5.3	
CHLORIDE	104		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	24		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	12			8-15	
UREA NITROGEN	18		MG/DL	7-25	
CREATININE	1.0		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	18			8-20	
URIC ACID	6.2		MG/DL	2.5 - 7.5	
CALCIUM	9.4		MG/DL	8.5-10.6	
PHOSPHORUS, INORGANIC	3.7		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.9		GM/DL	6.0-8.5	
ALBUMIN	4.4		GM/DL	3.2-5.5	
GLOBULIN	2.5		GM/DL	1.5-3.0	
A/G RATIO	1.8			1.1-2.2	
CALCIUM, IONIZED	4.2		MG/DL	3.6-4.8	
BILIRUBIN, TOTAL	0.4		MG/DL	0.2-1.2	
[redacted]					
LACTATE DEHYDROGENASE	144		U/L	0 - 250	
AST (SGOT)	22		U/L	0-50	
ALT (SGPT)	26		U/L	0 - 55	
[redacted]			MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR [redacted] YEARS OLD OR GREATER					
TRIGLYCERIDES	78		MG/DL	30-150	
IRON, TOTAL	71		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					MI
WHITE BLOOD CELLS			THOUSAND/CU.MM	3.9 - 10.0	
RED BLOOD CELLS	4.95		MILLIONS/CU.MM	3.90 - 5.20	
HEMOGLOBIN					
HEMATOCRIT	43.9		%	35.0 - 46.0	
MCV			CUBIC MICROMETERS	80.0 - 100.0	
MCH	29.6		PICOGRAMS	27.0 - 33.0	
MCHC			%	31.0 - 36.0	
RDW	13.2		UNITS	10.0 - 15.0	
PLATELET COUNT			THOUSAND/CU.MM	130 - 400	
NEUTROPHILS	58		%	40 - 75	
NEUTROPHILS, ABSOLUTE	2		THOUSAND/CU.MM	1.52 - 6.10	
LYMPHOCYTES	32		%	18 - 47	
LYMPHOCYTES, ABSOLUTE	1		THOUSAND/CU.MM	0.48 - 5.00	
MONOCYTES	5		%	0 - 10	
MONOCYTES, ABSOLUTE	0.18		THOUSAND/CU.MM	0.10 - 1.08	
EOSINOPHILS	3		%	0 - 6	

** REPORT CONTINUED ON NEXT PAGE **

INDICATES TESTING SITE SEE REVERSE SIDE †

ACCT. NO. [redacted]

SD *Clinical Laboratories*

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LAB NO. [redacted] PAGE 1

EG-FLORIDA INC
6244 S MILITARY TRAIL S-590
[redacted]Y BEACH, FL 33484

DATE COLLECTED 07/05/90 [redacted]
TIME COLLECTED 0630 AGE 52 SEX F
DATE ENTERED 07/06/90
DATE REPORTED 07/06/90 9:30AM
REPORT STATUS FINAL
[redacted]

** CONFIDENTIAL REPORT **
EA 00 ROUTE W3 STOP 150
OMMENTS:

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
HEMZYME PLUS/CBC/DIA					
CHEMZYME					K1
GLUCOSE	106		MG/DL	80 - 125	
SODIUM	139		MEQ/L	135-148	
POTASSIUM	4.4		MEQ/L	3.5-5.3	
CHLORIDE	104		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	26		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	[redacted]			[redacted]	
UREA NITROGEN	19		MG/DL	7-25	
CREATININE	1.0		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	19			8-20	
URIC ACID	4.2		MG/DL	2.5 - 7.5	
CALCIUM	9.7		MG/DL	8.5-10.5	
PHOSPHORUS, INORGANIC	3.7		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.9		GM/DL	6.0-8.5	
ALBUMIN	4.3		GM/DL	3.2-5.5	
GLOBULIN	2.6		GM/DL	1.5-3.8	
A/G RATIO	1.7			1.1-2.2	
CALCIUM, IONIZED	4.8		MG/DL	3.8-5.8	
BILIRUBIN, TOTAL	0.5		MG/DL	0.2-1.2	
ALKALINE PHOSPHATASE, TOTAL	100		U/L	20 - 140	
LACTATE DEHYDROGENASE	139		U/L	70 - 250	
ASPARTATE TRANSAMINASE (SGOT)	23		U/L	0-50	
ALANINE AMINOTRANSFERASE (SGPT)	29		U/L	0 - 55	
CHOLESTEROL, TOTAL	[redacted]		MG/DL	0 - 199	
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES	147		MG/DL	20-190	
IRON, TOTAL	130		MCG/DL	[redacted]	
CBC, AUTOMATED, W/DIFF	NO SPECIMEN RECEIVED				
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	50 L		MG/DL	[redacted]	MI
DESIRABLE LEVELS OF THE CHOLESTEROL ARE: MALE GREATER THAN 35 FEMALE GREATER THAN 35					
LDL CHOLESTEROL	210 H		MG/DL	LESS THAN 130	
** REPORT CONTINUED ON NEXT PAGE **					

INDICATES TESTING SITE SEE REVERSE SIDE†

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ACCT. NO.

LAB NO. PAGE

DATE COLLECTED [redacted]

TIME COLLECTED

DATE ENTERED 44 M

DATE REPORTED

REPORT STATUS FINAL

ROUTE STOP

COMMENTS:

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEMZYME PLUS/CBC/DIA					
CHEMZYME					M1
GLUCOSE	95		MG/DL	70 - 115	
SODIUM	140		MEQ/L	135-148	
POTASSIUM	4.8		MEQ/L	3.5-5.3	
CHLORIDE	105		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	27		MEQ/L	24-32	
ELECTROLYTIC BALANCE	8			5-15	
BUN/CREATININE RATIO	16		MG/DL	7-25	
CREATININE	1.3		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	[illegible]			8-20	
URIC ACID	6.3		MG/DL	4.0-8.5	
CALCIUM	9.8		MG/DL	8.5-10.5	
PHOSPHORUS, INORGANIC	3.3		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.4		GM/DL	6.0-8.5	
ALBUMIN	4.2		GM/DL	3.2-5.5	
GLOBULIN	2.2		GM/DL	1.5-3.8	
A/G RATIO	1.9			1.1-2.7	
CALCIUM, IONIZED	4.4		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.4		MG/DL	0.2-1.2	
ALKALINE PHOSPHATASE, TOTAL	54		U/L	20 - 140	
LACTATE DEHYDROGENASE	139		U/L	0 - 250	
ASPARTATE TRANSAMINASE (SGOT)	17		U/L	0-50	
ALANINE AMINOTRANSFERASE (SGPT)	18		U/L	0 - 50	
[redacted]			MG/DL	0 - 199	
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES	300 HIGH		MG/DL	20-150	M
THYROXINE, TOTAL	8.4		MCG/DL	4.0 - 11.0	
REC, PLATELET CT & DIFF					M1
WHITE BLOOD CELLS	5.5		THOUSAND/CU.MM.	3.8 - 10.8	
RED BLOOD CELLS	4.87		MILLION/CU.MM.	4.20 - 5.80	
HEMOGLOBIN (HB)	15.2		GM/DL	13.0 - 17.2	
HEMATOCRIT	47.6		%	41.0 - 50.0	
MCV	97.7		FEMTOLITERS	80.0 - 100.0	
MCH	31.1		PICOGRAMS	27.0 - 33.0	
MCHC	34.7		%	32.0 - 36.0	
RDW	12.5		UNITS	10.0 - 15.0	
PLATELET COUNT	212		THOUSAND/CU.MM.	130 - 400	
NEUTROPHILS	58		%	40 - 75	
NEUTROPHILS, ABSOLUTE	3.21		THOUSAND/CU.MM.	1.52 - 8.10	

>> REPORT CONTINUED ON NEXT PAGE <<

† INDICATES TESTING SITE SEE REVERSE SIDE

ACCT. NO. [redacted]

SD Clinical Laboratories

[redacted]

PAGE 1

[redacted]
[redacted] FLORIDA INC
[redacted] 4 S MILITARY TRAIL S-590
[redacted] AY BEACH, FL 33484

** CONFIDENTIAL REPORT **
[redacted] 00 ROUTE [redacted] STOP [redacted]
IMMENTS: [redacted]

LAB NO. [redacted]
DATE COLLECTED 07/19/90 #
TIME COLLECTED 8:30A - AGE 44 SEX M
DATE ENTERED 07/19/90
DATE REPORTED 07/23/90 5137AM
REPORT STATUS FINAL
[redacted]

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
LIPID DISEASE PROFILE					
CHOLESTEROL, TOTAL		290 H	MG/DL	0 - 199	MI
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES		269 H	MG/DL	20-160	MI
LIPOPROTEIN PHENOTYPE INTERPRETATION					MI
INTERPRETATION: TYPE IV PHENOTYPE.					
PATTERN SHOWS A DENSE PRE-BETA LIPOPROTEIN FRACTION. NORMAL BETA AND ALPHA FRACTIONS AND NO CHYLOMICRONS. THIS PATTERN, ASSOCIATED WITH NORMAL OR SLIGHTLY ELEVATED CHOLESTEROL, ELEVATED TRIGLYCERIDES AND EITHER CLEAR OR CLOUDY SERUM, IS CONSISTENT WITH THE ABOVE.					
NOTE: PROPER INTERPRETATION OF LIPOPROTEIN PATTERNS BASED ON ELECTROPHORESIS CLASSIFICATION REQUIRES MAINTENANCE OF AN AMERICAN DIET FOR AT LEAST 2 DAYS AND NO FOOD INGESTION 12 - 14 HOURS BEFORE THE SPECIMEN IS COLLECTED. ABNORMAL RESULTS ARE FREQUENTLY CAUSED BY UNDERLYING CONDITIONS RATHER THAN A GENETIC PREDISPOSITION.					
APPEARANCE	CLEAR				
MALA SENGUPTA, M.D., PATHOLOGIST					
HDL CHOLESTEROL	[redacted]		MG/DL	0 - 199	MI
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES		269 H	MG/DL	20-160	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	14 L		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	202 H		MG/DL	LESS THAN 130	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

ACCT. NO. [redacted]

[redacted]

PAGE 1

[redacted]
ES-FLORIDA INC
6244 S MILITARY TRAIL S-590
[redacted]Y BEACH, FL 33484

LAB NO. [redacted]2911
TIME COLLECTED 09/28/90 [redacted]
DATE ENTERED 850AM AGE 44 SEX M
DATE REPORTED 09/28/90
REPORT STATUS 10/01/90 5:36AM
FINAL

* CONFIDENTIAL REPORT **
IEA [redacted] ROUTE [redacted] STOP [redacted]
MMENTS: [redacted]

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEM ENZYME PLUS/CBC/UA					
CHEMZYME					MI
GLUCOSE	103		MG/DL	70 - 115	
SODIUM	142		MEQ/L	135 146	
POTASSIUM	3.9		MEQ/L	3.5-5.3	
CHLORIDE	109		MEQ/L	75-110	
CARBON DIOXIDE CONTENT	25		MEQ/L	20 - 32	
ELECTROLYTE BALANCE	8			5-15	
UREA NITROGEN	18		MG/DL	7-25	
CREATININE	1.2		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	15			8-20	
URIC ACID	6.2		MG/DL	4.0 8.5	
CALCIUM	9.3		MG/DL	8.5-10.6	
PHOSPHORUS, INORGANIC	3.6		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.4		GM/DL	6.0-8.5	
ALBUMIN	4.0		GM/DL	3.2-5.5	
GLOBULIN	2.4		GM/DL	1.5-3.8	
A/G RATIO	1.7			1.1-2.2	
CALCIUM, IONIZED	4.3		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.7		MG/DL	0.2-1.2	
ALK PHOS, TOTAL	51		U/L	20 - 140	
LACTATE DEHYDROGENASE	158		U/L	0 - 250	
AST (SGOT)	21		U/L	0-50	
ALT (SGPT)	30		U/L	0 - 55	
[redacted]			MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	222 H		MG/DL	20-160	
IRON, TOTAL	128		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					MI
WHITE BLOOD CELLS	5.8		THOUSAND/CU.MM.	3.8 - 10.8	
RED BLOOD CELLS	4.65		MILLIONS/CU.MM.	4.40 - 5.80	
HEMOGLOBIN (B)	14.2		GM/DL	13.8 - 17.2	
HEMATOCRIT	41.8		%	41.0 - 50.0	
MCV	90.0		FEMTOLITERS	80.0 - 100.0	
MCH	30.6		PICOGRAMS	27.0 - 33.0	
MCHC	34.1		%	32.0 - 36.0	
RDW	10.4		UNITS	10.0 - 15.0	
PLATELET COUNT	154		THOUSAND/CU.MM.	130 - 400	
NEUTROPHILS	58		%	40 - 75	
NEUTROPHILS, ABSOLUTE	3.35		THOUSAND/CU.MM.	1.52 - 8.10	
LYMPHOCYTES	32		%	18 - 47	
LYMPHOCYTES, ABSOLUTE	1.84		THOUSAND/CU.MM.	0.68 - 5.07	
MONOCYTES	6		%	0 - 10	
MONOCYTES, ABSOLUTE	0.33		THOUSAND/CU.MM.	0.10 - 1.08	
EOSINOPHILS	3		%	0 - 8	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

[redacted]

ACCT. NO. 05411

LAB NO. 2502921 PAGE 1

[redacted] FLORIDA INC
14244 S MILITARY TRAIL S-590
DELRAY BEACH, FL 33484

DATE COLLECTED 08/30/90 [redacted]
TIME COLLECTED 0800 AGE 56 SEX F
DATE ENTERED 08/30/90
DATE REPORTED 08/31/90 5:27AM
REPORT STATUS FINAL

** CONFIDENTIAL REPORT **

EA 00 ROUTE W3 STOP 150

0830901171362695IP

MMENTS:

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEMZYME PLUS/CBC/UA					
CHEMZYME					MI
GLUCOSE	89		MG/DL	80 - 125	
SODIUM	142		MEQ/L	135-148	
POTASSIUM	4.3		MEQ/L	3.5-5.3	
CHLORIDE	104		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	28		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	10			5-15	
UREA NITROGEN	17		MG/DL	7-25	
CREATININE	1.2		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	14			8-20	
URIC ACID	3.4		MG/DL	2.5 - 7.5	
CALCIUM	9.6		MG/DL	8.5-10.6	
PHOSPHORUS, INORGANIC	3.2		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.9		GM/DL	6.0-8.5	
ALBUMIN	3.9		GM/DL	3.2-5.5	
GLOBULIN	3.0		GM/DL	1.5-3.8	
A/G RATIO	1.3			1.1-2.2	
CALCIUM, IONIZED	4.3		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.5		MG/DL	0.2-1.2	
ALKALINE PHOSPHATASE, TOTAL	77		U/L	20 - 140	
LACTATE DEHYDROGENASE	126		U/L	0 - 250	
ASPARTATE TRANSAMINASE (SGOT)	22		U/L	0-50	
ALANINE AMINOTRANSFERASE (SGPT)	14		U/L	0 - 55	
CHOLESTEROL, TOTAL	[redacted]	[redacted]	MG/DL	0 - 199	
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES	239 H		MG/DL	20-190	
IRON, TOTAL	66		MCG/DE	40 - 150	
CBC, PLATELET CT & DIFF					MI
WHITE BLOOD CELLS	3.7 L		THOUSAND/CU.MM.	3.8 - 10.8	
RED BLOOD CELLS	4.06		MILLIONS/CU.MM.	3.90 - 5.20	
HEMOGLOBIN (B)	12.3		GM/DL	12.0 - 15.6	
HEMATOCRIT	36.5		%	35.0 - 46.0	
MCV	89.9		FEMTOLITERS	80.0 - 100.0	
MCH	30.3		PICOGRAMS	27.0 - 33.0	
MCHC	33.8		%	32.0 - 36.0	
RDW	10.8		UNITS	10.0 - 15.0	
PLATELET COUNT	141		THOUSAND/CU.MM.	130 - 400	
NEUTROPHILS	50		%	40 - 75	
NEUTROPHILS, ABSOLUTE	1.88		THOUSAND/CU.MM.	1.52 - 8.10	

>> REPORT CONTINUED ON NEXT PAGE <<

† INDICATES TESTING SITE SEE REVERSE SIDE

ACCT. NO. 25411

Clinical Laboratories

[redacted]

ES-FLORIDA INC
6244 S MILITARY TRAIL S-590
F [redacted]AY BEACH, FL 33484

LAB NO. 2502756 PAGE 1
DATE COLLECTED 09/04/90 [redacted]
TIME COLLECTED 0900 AGE 56 SEX F
DATE ENTERED 09/04/90
DATE REPORTED 09/05/90 5:19AM
REPORT STATUS FINAL
0904901134Z/332582P

* CONFIDENTIAL REPORT **
EA 00 ROUTE W3 STOP 150
MMENTS: "FASTING SPECIMEN"

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
A.R.E. PANEL #2					
CHOLESTEROL, TOTAL	[redacted]		MG/DL	0 - 199	MI
DESIRABLE ADULT LEVEL FOR CHOLESTEROL IS LESS THAN 200 MG/DL.					
TRIGLYCERIDES	234	H	MG/DL	20-190	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	35	L	MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	165	H	MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	7.06				

****

CORONARY HEART DISEASE RISK TABLE

	RELATIVE RISK	T/HDL CHOL RATIO
MEN	0.5 AVERAGE	3.43
	AVERAGE	4.97
	2 X AVERAGE	9.55
	3 X AVERAGE	23.39
WOMEN	0.5 AVERAGE	3.27
	AVERAGE	4.44
	2 X AVERAGE	7.05
	3 X AVERAGE	11.04

****

>> END OF REPORT <<

Craig C. Fuller 9/5/90

INDICATES TESTING SITE SEE REVERSE SIDE †

ACCT. NO. 23411

Clinical Laboratories

[redacted]

LAB NO. 2502782 PAGE 1

DATE COLLECTED 09/07/90

TIME COLLECTED 0800

DATE ENTERED 09/07/90

DATE REPORTED 09/08/90 9:03AM

REPORT STATUS FINAL

AGE 56 SEX F

S-FLORIDA INC
5244 S MILITARY TRAIL S-590
[illegible]Y BEACH, FL 33484

** CONFIDENTIAL REPORT **

[illegible] ROUTE W3 STOP 160

0907901216S/6516575P

AMENTS:

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
A-FLE...PANEL #2					
CHOLESTEROL, TOTAL	[redacted]		MG/DL	LESS THAN 200	MI
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	243 H		MG/DL	20-190	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	35 L		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45					
FEMALE GREATER THAN 55					
LDL CHOLESTEROL	186 H		MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	7.71				

****

CORONARY HEART DISEASE RISK TABLE

	RELATIVE RISK	T/HDL CHOL RATIO
MEN	0.5 AVERAGE	3.43
	AVERAGE	4.97
	2 X AVERAGE	9.55
	3 X AVERAGE	23.39
WOMEN	0.5 AVERAGE	3.27
	AVERAGE	4.44
	2 X AVERAGE	7.05
	3 X AVERAGE	11.04

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>> END OF REPORT <<

† INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

[redacted]

ACCT. NO. 25411

LAB NO. 2955931 PAGE 1

ES-FLORIDA INC
[redacted] 11/12/90
44 S MILITARY TRAIL S-590
AY BEACH, FL 33484

TIME COLLECTED 830 AGE 47 SEX F

DATE ENTERED 11/12/90

DATE REPORTED 11/13/90 5:16AM

REPORT STATUS FINAL

* CONFIDENTIAL REPORT **
A 00 ROUTE W3 STOP 160
MMENTS. *FASTING SPECIMEN*

11129012576/039506V

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
HEMZYME PLUS/CBC/UA					
CHEMZYME					MI
GLUCOSE	103		MG/DL	70 - 115	
SODIUM	144		MEQ/L	135 - 148	
POTASSIUM	3.8		MEQ/L	3.5 - 5.3	
CHLORIDE	104		MEQ/L	95 - 110	
CARBON DIOXIDE CONTENT	28		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	12			5-15	
UREA NITROGEN	19		MG/DL	7 - 25	
CREATININE	1.2		MG/DL	0.7 - 1.4	
BUN/CREATININE RATIO	16			8-20	
URIC ACID	4.2		MG/DL	2.5 - 7.5	
CALCIUM	9.3		MG/DL	8.5 - 10.6	
PHOSPHORUS, INORGANIC	3.5		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.7		GM/DL	6.0-8.5	
ALBUMIN	3.8		GM/DL	3.2-5.5	
GLOBULIN, TOTAL	2.9		GM/DL	1.5-3.8	
A/G RATIO	1.3			1.1-2.2	
CALCIUM, IONIZED	4.2		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.7		MG/DL	0.2 - 1.2	
ALK PHOS, TOTAL	81		U/L	20 - 140	
LACTATE DEHYDROGENASE	147		U/L	0 - 250	
AST (SGOT)	52 H	NCS	U/L	0-50	
ALT (SGPT)	46		U/L	0 - 55	
[redacted]			MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	170 H		MG/DL	20-160	
IRON, TOTAL	68		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					MI
WHITE BLOOD CELLS	5.2		THOUSAND/CU.MM	3.8 - 10.8	
RED BLOOD CELLS	4.40		MILLIONS/CU.MM	3.90 - 5.20	
HEMOGLOBIN (B)	13.2		GM/DL	12.0 - 15.6	
HEMATOCRIT	39.2		%	35.0 - 46.0	
MCV	89.0		FEMTOLITERS	80.0 - 100.0	
MCH	30.0		PICOGRAMS	27.0 - 33.0	
MCHC	33.7		%	32.0 - 36.0	
RDW	12.5		UNITS	10.0 - 15.0	
PLATELET COUNT	142		THOUSAND/CU.MM	130 - 400	
NEUTROPHILS	53		%	40 - 75	
NEUTROPHILS, ABSOLUTE	2.78		THOUSAND/CU.MM	1.52 - 8.10	
LYMPHOCYTES	37		%	18 - 47	
LYMPHOCYTES, ABSOLUTE	1.88		THOUSAND/CU.MM	0.68 - 5.07	
MONOCYTES	6		%	0 - 10	
MONOCYTES, ABSOLUTE	0.28		THOUSAND/CU.MM	0.10 - 1.08	
EOSINOPHILS	3		%	0 - 6	

>> REPORT CONTINUED ON NEXT PAGE <<

11/13/90

INDICATES TESTING SITE SEE REVERSE SIDE †

Clinical Laboratories

ACCT. NO. 25411

PES-FLORIDA INC
16244 S MILITARY TRAIL S-590
DELRAY BEACH, FL 33484

** CONFIDENTIAL REPORT **
AREA 00 ROUTE W3 STOP 160
COMMENTS: FASTING

LAB NO. 2502801 PAGE 1
DATE COLLECTED 09/19/90
TIME COLLECTED 0830 AGE 47 SEX M
DATE ENTERED 09/19/90
DATE REPORTED 09/20/90 7:44AM
REPORT STATUS FINAL
09199011339/702808P

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEMZYME PLUS/CBC/DA					
CHEMZYME					MI
GLUCOSE	97		MG/DL	70 - 115	
SODIUM	139		MEQ/L	135-148	
POTASSIUM	4.2		MEQ/L	3.5-5.3	
CHLORIDE	103		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	27		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	9			5-15	
UREA NITROGEN	13		MG/DL	7-25	
CREATININE	1.2		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	11			8-20	
URIC ACID	6.6		MG/DL	4.0-8.5	
CALCIUM	8.9		MG/DL	8.5-10.6	
PHOSPHORUS, INORGANIC	2.8		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.7		GM/DL	6.0-8.5	
ALBUMIN	4.0		GM/DL	3.2-5.5	
GLOBULIN	2.7		GM/DL	1.5-3.8	
A/G RATIO	1.5			1.1-2.2	
CALCIUM, IONIZED	4.0		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.6		MG/DL	0.2-1.2	
ALK PHOS, TOTAL	55		U/L	20 - 140	
LACTATE DEHYDROGENASE	125		U/L	0 - 250	
AST (SGOT)	21		U/L	0-50	
ALT (SGPT)	22		U/L	0 - 55	
[redacted]	[redacted]		MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	162 H		MG/DL	20-160	
IRON, TOTAL	102		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					MI
WHITE BLOOD CELLS	5.0		THOUSAND/CU.MM.	3.8 - 10.8	
RED BLOOD CELLS	4.49		MILLIONS/CU.MM.	4.40 - 5.80	
HEMOGLOBIN (B)	13.8		GM/DL	13.6 - 17.2	
HEMATOCRIT	40.1 L		%	41.0 - 50.0	
MCV	89.3		FEMTOLITERS	80.0 - 100.0	
MCH	30.6		PICOGRAMS	27.0 - 33.0	
MCHC	34.3		%	32.0 - 36.0	
RDW	11.8		UNITS	10.0 - 15.0	
PLATELET COUNT	175		THOUSAND/CU.MM.	130 - 400	
NEUTROPHILS	51		%	40 - 75	
NEUTROPHILS, ABSOLUTE	2.54		THOUSAND/CU.MM.	1.52 - 8.10	
LYMPHOCYTES	39		%	18 - 47	
LYMPHOCYTES, ABSOLUTE	1.93		THOUSAND/CU.MM.	0.68 - 5.07	
MONOCYTES	5		%	0 - 10	
MONOCYTES, ABSOLUTE	0.31		THOUSAND/CU.MM.	0.10 - 1.08	
EOSINOPHILS	3		%	0 - 6	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

ACCT. NO. 25411

PES FLORIDA INC
1[redacted]S MILITARY TRAIL S-590
DELRAY BEACH FL 33484

** CONFIDENTIAL REPORT **
AREA 00 ROUTE W3 STOP 160
COMMENTS:

LAB NO. 2502087
DATE COLLECTED 09/24/90
TIME COLLECTED 0900
DATE ENTERED 09/24/90
DATE REPORTED 09/25/90 5:28AM
REPORT STATUS FINAL
0924011750/710427P

[redacted]
PAGE 1
AGE 47 SEX M

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
C.A.R.E. PANEL #2					
CHOLESTEROL, TOTAL	[redacted]		MG/DL	LESS THAN 200 MI	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	137		MG/DL	30-160	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	62		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	228	H	MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	5.11				

****
CORONARY HEART DISEASE RISK TABLE

	RELATIVE RISK	T/HDL CHOL RATIO
MEN	0.5 AVERAGE	3.43
	AVERAGE	4.97
	2 X AVERAGE	9.55
	3 X AVERAGE	23.39
WOMEN	0.5 AVERAGE	3.27
	AVERAGE	4.44
	2 X AVERAGE	7.05
	3 X AVERAGE	11.04

****

>> END OF REPORT <<

INDICATES TESTING SITE SEE REVERSE SIDE †

SD Clinical Laboratories

[redacted]

ACCT. NO. 25411

LAB NO. 2502805 PAGE 1

ES-FLORIDA INC
6[illegible] S MILITARY TRAIL S-590
EL...Y BEACH, FL 33484

DATE COLLECTED 09/27/90 [redacted]
TIME COLLECTED 9AM AGE 47 SEX M
DATE ENTERED 09/27/90
DATE REPORTED 09/28/90 5:32AM
REPORT STATUS FINAL

** CONFIDENTIAL REPORT **
IEA 00 ROUTE W3 STOP 160
OMMENTS: "FASTING SPECIMEN"

09279012433/739146P

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
LIPID PANEL #2					
[redacted]		[redacted]	MG/DL	LESS THAN 200	MI
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	115		MG/DL	20-160	MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	62		MG/DL		MI
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	224	H	MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	4.98				

****
CORONARY HEART DISEASE RISK TABLE

	RELATIVE RISK	T/HDL CHOL RATIO
MEN	0.5 AVERAGE	3.43
	AVERAGE	4.97
	2 X AVERAGE	9.55
	3 X AVERAGE	23.39
WOMEN	0.5 AVERAGE	3.27
	AVERAGE	4.44
	2 X AVERAGE	7.05
	3 X AVERAGE	11.04

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>> END OF REPORT <<

INDICATES TESTING SITE SEE REVERSE SIDE †

Clinical Laboratories

ACCT. NO. 25411 PH [redacted]

LAB NO. [redacted] PAGE 1

ES-FLORIDA INC
[redacted] S MILITARY TRAIL S-590
E[redacted]Y BEACH, FL 33484

TIME COLLECTED 8 AM AGE 47 SEX M
DATE ENTERED 12/05/90
DATE REPORTED 12/06/90 5:25AM
REPORT STATUS FINAL

** CONFIDENTIAL REPORT **
EA 00 ROUTE W3 STOP 160 12059012547/138341V
IMMENTS: FASTING

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
HEMZYME PLUS/CRC/UA					
CHEMZYME					MI
GLUCOSE	107		MG/DL	70 - 115	
SODIUM	140		MEQ/L	135 - 148	
POTASSIUM	4.4		MEQ/L	3.5 - 5.3	
CHLORIDE	105		MEQ/L	95 - 110	
CARBON DIOXIDE CONTENT	27		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	8			5-15	
UREA NITROGEN	11		MG/DL	7 - 25	
CREATININE	1.1		MG/DL	0.7 - 1.4	
BUN/CREATININE RATIO	10			8-20	
URIC ACID	4.7		MG/DL	4.0-8.5	
CALCIUM	9.1		MG/DL	8.5 - 10.6	
PHOSPHORUS, INORGANIC		2.4 L	MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.7		GM/DL	6.0-8.5	
ALBUMIN	4.0		GM/DL	3.2-5.5	
GLOBULIN, TOTAL	2.7		GM/DL	1.5-3.8	
A/G RATIO	1.5			1.1-2.2	
CALCIUM, IONIZED	4.1		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.7		MG/DL	0.2 - 1.2	
ALK PHOS, TOTAL	51		U/L	20 - 140	
LACTATE DEHYDROGENASE	115		U/L	0 - 250	
AST (SGOT)	14		U/L	0-50	
ALT (SGPT)	10		U/L	0 - 55	
[redacted]			MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	80		MG/DL	20-160	
IRON, TOTAL	90		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					MI
WHITE BLOOD CELLS	4.7		THOUSAND/CU.MM.	3.8 - 10.8	
RED BLOOD CELLS	4.54		MILLIONS/CU.MM.	4.40 - 5.80	
HEMOGLOBIN (B)	13.8		GM/DL	13.8 - 17.2	
HEMATOCRIT	41.2		%	41.0 - 50.0	
MCV	90.9		FEMTOLITERS	80.0 - 100.0	
MCH	30.5		PICOGRAMS	27.0 - 33.0	
MCHC	33.6		%	32.0 - 36.0	
RDW	11.4		UNITS	10.0 - 15.0	
PLATELET COUNT	168		THOUSAND/CU.MM.	130 - 400	
NEUTROPHILS	49		%	40 - 75	
NEUTROPHILS, ABSOLUTE	2.30		THOUSAND/CU.MM.	1.52 - 8.10	
LYMPHOCYTES	41		%	18 - 47	
LYMPHOCYTES, ABSOLUTE	1.94		THOUSAND/CU.MM.	0.68 - 5.07	
MONOCYTES	7		%	0 - 10	
MONOCYTES, ABSOLUTE	0.32		THOUSAND/CU.MM.	0.10 - 1.08	
EOSINOPHILS	2		%	0 - 6	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

[redacted]

ACCT. NO. 25411

LAB NO. 25[illegible]849 PAGE 1

[redacted] COLLECTION 10/05/90

TIME COLLECTED 0800AM AGE 58 SEX F

DATE ENTERED 10/05/90

DATE REPORTED 10/08/90 5:47AM

REPORT STATUS FINAL

[redacted]

CS-FLORIDA INC
7244 S MILITARY TRAIL S-590
DAY BEACH, FL 33484

** CONFIDENTIAL REPORT **

STAT 00 ROUTE 83 STOP 160

COMMENTS: FASTING

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEM-ENZYME PLUS/CBC/DA					
CHEM-ENZYME					61
GLUCOSE	85		MG/DL	80 - 125	
SODIUM	136		MEQ/L	135-148	
POTASSIUM	4.0		MEQ/L	3.5-5.3	
CHLORIDE	102		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	24		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	13			5-15	
UREA NITROGEN	13		MG/DL	7-25	
CREATININE	1.1		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	12			8-20	
URIC ACID	5.8		MG/DL	2.5 - 7.5	
CALCIUM	9.2		MG/DL	8.5-10.6	
PHOSPHORUS, INORGANIC	4.1		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.6		GM/DL	6.0-8.5	
ALBUMIN	3.9		GM/DL	3.2-5.5	
GLOBULIN	2.7		GM/DL	1.5-3.8	
A/G RATIO	1.4			1.1-2.2	
CALCIUM, IONIZED	4.2		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.4		MG/DL	0.2-1.2	
ALK PHOS, TOTAL	72		U/L	20-140	
LACTATE DEHYDROGENASE	178		U/L	0 - 250	
AST (SGOT)	17		U/L	0-50	
ALT (SGPT)	9		U/L	0 - 55	
[redacted]	[redacted]	[redacted]	MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	87		MG/DL	20-190	
IRON, TOTAL	109		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					M1
WHITE BLOOD CELLS	4.3		THOUSAND/CU.MM	3.8 - 10.8	
RED BLOOD CELLS	3.74 L		MILLIONS/CU.MM	3.90 - 5.20	
HEMOGLOBIN (B)	11.4 L		GM/DL	12.0 - 15.6	
HEMATOCRIT	34.0 L		%	35.0 - 46.0	
MCV	90.8		FEMTOLITERS	80.0 - 100.0	
MCH	30.4		PICOGRAMS	27.0 - 33.0	
MCHC	33.5		%	32.0 - 36.0	
RDW	14.1		UNITS	10.0 - 15.0	
PLATELET COUNT	260		THOUSAND/CU.MM	130 - 400	
NEUTROPHILS	48		%	40 - 75	
NEUTROPHILS, ABSOLUTE	2.09		THOUSAND/CU.MM	1.52 - 8.10	
LYMPHOCYTES	40		%	18 - 47	
LYMPHOCYTES, ABSOLUTE	1.73		THOUSAND/CU.MM	0.68 - 5.07	
MONOCYTES	7		%	0 - 10	
MONOCYTES, ABSOLUTE	0.30		THOUSAND/CU.MM	0.10 - 1.08	
EOSINOPHILS	5		%	0 - 6	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE

ES-FLORIDA INC
6244 S MILITARY TRAIL S-590
E VY BEACH, FL 33484

* CONFIDENTIAL REPORT **

EA 00 ROUTE WS STOP 160

MMENTS: FASTING

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
A.R.F. PANEL #2					
CHOLESTEROL, TOTAL	[redacted]		MG/DL	LESS THAN 200 MI	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	85		MG/DL	20-190	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	56		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL		216 H	MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	5.16				
********** CORONARY HEART DISEASE RISK TABLE **********					
RELATIVE RISK	T/HDL CHOL RATIO				
MEN 0.5 AVERAGE	3.43				
AVERAGE	4.97				
2 X AVERAGE	9.55				
3 X AVERAGE	23.39				
WOMEN 0.5 AVERAGE	3.27				
AVERAGE	4.44				
2 X AVERAGE	7.05				
3 X AVERAGE	11.04				
**********					
ERRITIN	[redacted]		NG/ML		MI
		LESS THAN 10			
		CHILDREN (PREPUBERTAL):		8 - 140	
		FEMALES (PREMENOPAUSAL):		LESS THAN 235	
		FEMALES (POST MENOPAUSAL):		6 - 270	
		MALES:		15 - 445	
RON, TOTAL, IBC & %					MI
URATION (S)					
ON, TOTAL	78		MCG/DL	40 - 150	
IRON BINDING CAPACITY	371		MCG/DL	250 - 400	

>> REPORT CONTINUED ON NEXT PAGE <<

10/12/90

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

[redacted]

ACCT. NO. 25411

ES-FLORIDA INC
6244 S MILITARY TRAIL S-590
E ...Y BEACH, FL 33484

** CONFIDENTIAL REPORT **
EA 00 ROUTE W3 STOP 160
MMENTS:

LAB NO. 2502819 PAGE 1
DATE COLLECTED 10/12/90
TIME COLLECTED 0900
DATE ENTERED 10/12/90
DATE REPORTED 10/15/90 5:34AM
REPORT STATUS FINAL
1012901264?/007199P

[redacted] AGE 58 SEX F

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
A.R.E. PANEL #2					
CHOLESTEROL, TOTAL	[redacted]		MG/DL	LESS THAN 200	MI
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	110		MG/DL	20-190	MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	58		MG/DL		MI
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE:			MALE	GREATER THAN 45	
			FEMALE	GREATER THAN 55	
LDL CHOLESTEROL	227	H	MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	5.29				

****
CORONARY HEART DISEASE RISK TABLE

	RELATIVE RISK	T/HDL CHOL RATIO
MEN	0.5 AVERAGE	3.43
	AVERAGE	4.97
	2 X AVERAGE	9.55
	3 X AVERAGE	23.39
WOMEN	0.5 AVERAGE	3.27
	AVERAGE	4.44
	2 X AVERAGE	7.05
	3 X AVERAGE	11.04

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>> END OF REPORT <<

C Price 10/16/90

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

[redacted]

ACCT. NO. 25411

LAB NO. 2955949

PAGE 1

PES-FLORIDA INC
1 14 S MILITARY TRAIL S-590
DELRAY BEACH, FL 33484

DATE COLLECTED [redacted] 12/21/90 [redacted] SEX
TIME COLLECTED 0930
DATE ENTERED 12/21/90 90032
DATE REPORTED 12/24/90 5133AM
REPORT STATUS FINAL

** CONFIDENTIAL REPORT **
EA 00 ROUTE W3 STOP 160
MMENTS: FASTING

1221901814/2130140

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEMZYME PLUS/CBC+/UA					
CHEMZYME					MI
GLUCOSE	94		MG/DL	70 - 115	
SODIUM	143		MEQ/L	135 - 148	
POTASSIUM	3.8		MEQ/L	3.5 - 5.3	
CHLORIDE	110		MEQ/L	95 - 110	
CARBON DIOXIDE CONTENT	24		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	9			5-15	
UREA NITROGEN	11		MG/DL	7 - 25	
CREATININE	1.2		MG/DL	0.7 - 1.4	
BUN/CREATININE RATIO	9			8-20	
URIC ACID	4.9		MG/DL	4.0-8.5	
CALCIUM	8.9		MG/DL	8.5 - 10.6	
PHOSPHORUS, INORGANIC	3.2		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.6		GM/DL	6.0 - 8.5	
ALBUMIN	3.9		GM/DL	3.2-5.5	
GLOBULIN, TOTAL	2.7		GM/DL	1.5-3.8	
A/G RATIO	1.4			1.1-2.2	
CALCIUM, IONIZED	4.1		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.3		MG/DL	0.2 - 1.2	
ALK PHOS, TOTAL	75		U/L	20 - 140	
LACTATE DEHYDROGENASE	200		U/L	0 - 250	
AST (SGOT)	18		U/L	0-50	
ALT (SGPT)	7		U/L	0 - 55	
[redacted]			MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	57		MG/DL	20 - 160	
IRON, TOTAL	45		MCG/DL	40 - 150	
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	63		MG/DL		MI
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	138 H		MG/DL	LESS THAN 130	
>> REPORT CONTINUED ON NEXT PAGE <<					

Craig Clin 12/27/90

INDICATES TESTING SITE SEE REVERSE SIDE †

Clinical Laboratories

ACCT. NO. 25411

[redacted]

LAB NO. 2255870 PAGE 1

PES-FLORIDA INC
4244 S MILITARY TRAIL S-590
DELRAY BEACH, FL 33484

[redacted] 10/1[redacted]

TIME COLLECTED 10AM AGE 61 SEX F

DATE ENTERED 10/18/90

DATE REPORTED 10/19/90 6:29AM

REPORT STATUS FINAL

** CONFIDENTIAL REPORT **

EA 00 ROUTE W3 STOP 160

1018901307S/832656P

COMMENTS: 'FASTING SPECIMEN'

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEMZYME PLUS/CBC/UA					
CHEMZYME					MI
GLUCOSE	98		MG/DL	80 - 125	
SODIUM	142		MEQ/L	135-148	
POTASSIUM	4.5		MEQ/L	3.5-5.3	
CHLORIDE	107		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	25		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	10			5-15	
UREA NITROGEN	15		MG/DL	7-25	
CREATININE	1.1		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	14			8-20	
URIC ACID	4.4		MG/DL	2.5 - 7.5	
CALCIUM	8.8		MG/DL	8.5-10.6	
PHOSPHORUS, INORGANIC	3.8		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.6		GM/DL	6.0-8.5	
ALBUMIN	3.8		GM/DL	3.2-5.5	
GLOBULIN, TOTAL	2.8		GM/DL	1.5-3.8	
A/G RATIO	1.4			1.1-2.2	
CALCIUM, IONIZED	4.0		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.3		MG/DL	0.2-1.2	
ALK PHOS, TOTAL	55		U/L	20 - 140	
LACTATE DEHYDROGENASE	153		U/L	0 - 250	
AST (SGOT)	20		U/L	0-50	
ALT (SGPT)	16		U/L	0 - 55	
[redacted]		[redacted]	MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	110		MG/DL	20-120	
IRON, TOTAL	80		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					MI
WHITE BLOOD CELLS	4.1		THOUSAND/CU.MM	3.8 - 10.8	
RED BLOOD CELLS	3.81 L		MILLIONS/CU.MM	3.90 - 5.20	
HEMOGLOBIN (Hb)	11.8 L		GM/DL	12.0 - 15.6	
HEMATOCRIT	34.7 L		%	35.0 - 46.0	
MCV	91.1		FEMTOLITERS	80.0 - 100.0	
MCH	31.0		PICOGRAMS	27.0 - 33.0	
MCHC	34.0		%	32.0 - 36.0	
RDW	11.3		UNITS	10.0 - 15.0	
PLATELET COUNT	238		THOUSAND/CU.MM	130 - 400	
NEUTROPHILS	43		%	40 - 75	
NEUTROPHILS, ABSOLUTE	1.72		THOUSAND/CU.MM	1.52 - 8.10	
LYMPHOCYTES	46		%	18 - 47	
LYMPHOCYTES, ABSOLUTE	1.86		THOUSAND/CU.MM	0.68 - 5.07	
MONOCYTES	4		%	0 - 10	
MONOCYTES, ABSOLUTE	0.17		THOUSAND/CU.MM	0.10 - 1.08	
EOSINOPHILS	6		%	0 - 6	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE †

'ES-FLORIDA INC
6744 S MILITARY TRAIL S-590
E, IY BEACH, FL 33484

** CONFIDENTIAL REPORT **

REA 00 ROUTE W3 STOP 160

OMMENTS:

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
A.R.E. PANEL #2					
CHOLESTEROL, TOTAL	[redacted]		MG/DL	LESS THAN 200	MI
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	151		MG/DL	20-190	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	43 L		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	175 H		MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	5.77				
********** CORONARY HEART DISEASE RISK TABLE **********					
RELATIVE RISK T/HDL CHOL RATIO					
MEN 0.5 AVERAGE	3.43				
AVERAGE	4.97				
2 X AVERAGE	9.55				
3 X AVERAGE	23.39				
WOMEN 0.5 AVERAGE	3.27				
AVERAGE	4.44				
2 X AVERAGE	7.05				
3 X AVERAGE	11.04				
**********					
URINALYSIS, ROUTINE					MI
APPEARANCE	YELLOW CLEAR				
SPECIFIC GRAVITY	1.015			1.001 - 1.035	
PH, URINE	6.5			4.6 - 8.0	
PROTEIN, TOTAL (U) QL	NEGATIVE		MG/DL	NEGATIVE	
GLUCOSE (U) QL	NEGATIVE		MG/DL	NEGATIVE	
KETONES, URINE	NEGATIVE		MG/DL	NEGATIVE	
BILIRUBIN	NEGATIVE			NEGATIVE	
NITRITE	NEGATIVE			NEGATIVE	
LEUKOCYTE ESTERASE	NEGATIVE			NEGATIVE	
BLOOD	NEGATIVE			NEGATIVE	

>> REPORT CONTINUED ON NEXT PAGE <<

Craig Lee 10/24/90

INDICATES TESTING SITE SEE REVERSE SIDE †

JJD Clinical Laboratories

ACCT. NO. 25411

ES-FLORIDA INC
6[illegible] S MILITARY TRAIL S-590
[illegible]AY BEACH, FL 33484

* CONFIDENTIAL REPORT **
IEA 00 ROUTE W3 STOP 160
)MMENTS: "FASTING SPECIMEN"

LAB NO. 2955889 PAGE 1
[redacted]
TIME COLLECTED 9AM AGE 61 SEX F
DATE ENTERED 10/25/90
DATE REPORTED 10/26/90 5:17AM
REPORT STATUS FINAL
10259011553/863760P

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
.A.R.E. PANEL #2					
[redacted]		[redacted]	MG/DL	LESS THAN 200	MI
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	145		MG/DL	20-190	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN		48 L	MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE:		MALE GREATER THAN 45 FEMALE GREATER THAN 55			
LDL CHOLESTEROL		188 H	MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	5.52				

****
CORONARY HEART DISEASE RISK TABLE

	RELATIVE RISK	T/HDL CHOL RATIO
MEN	0.5 AVERAGE	3.43
	AVERAGE	4.97
	2 X AVERAGE	9.55
	3 X AVERAGE	23.39
WOMEN	0.5 AVERAGE	3.27
	AVERAGE	4.44
	2 X AVERAGE	7.05
	3 X AVERAGE	11.04

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[redacted]

>> END OF REPORT <<

Craig Chevalier

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

[redacted]

ACCT. NO. 25411

LAB NO. [redacted]2856011 PAGE 1

[redacted] 12/27/90

TIME COLLECTED 0930 AGE 61 SEX F

DATE ENTERED 12/27/90 22

DATE REPORTED 12/28/90 5:21AM

REPORT STATUS FINAL

122790126?4/2271470

?ES-FLORIDA INC
?744 S MILITARY TRAIL S-590
RAY BEACH, FL 33484

** CONFIDENTIAL REPORT **

EA 00 ROUTE WJ STOP 360

MMENTS: FASTING

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
REMZYME PLUS/CBC+/UA					
CREMZYME					MI
GLUCOSE	101		MG/DL	70 - 125	
SODIUM	141		MEQ/L	135 - 148	
POTASSIUM	4.3		MEQ/L	3.5 - 5.3	
CHLORIDE	108		MEQ/L	75 - 110	
CARBON DIOXIDE CONTENT	27		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	6			5-15	
UREA NITROGEN	12		MG/DL	7 - 25	
CREATININE	1.0		MG/DL	0.7 - 1.4	
BUN/CREATININE RATIO	12			8-20	
URIC ACID	4.5		MG/DL	2.5 - 7.5	
CALCIUM	8.9		MG/DL	8.5 - 10.6	
PHOSPHORUS, INORGANIC	3.4		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.3		GM/DL	6.0-8.5	
ALBUMIN	3.8		GM/DL	3.2-5.5	
GLOBULIN, TOTAL	2.5		GM/DL	1.5-3.8	
A/G RATIO	1.5			1.1-2.2	
CALCIUM, IONIZED	4.2		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.2		MG/DL	0.2 - 1.2	
ALK PHOS, TOTAL	50		U/L	20 - 140	
LACTATE DEHYDROGENASE	179		U/L	0 - 250	
AST (SGOT)	22		U/L	0-50	
ALT (SGPT)	21		U/L	0 - 55	
[redacted]	[redacted]		MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	78		MG/DL	20-190	
IRON, TOTAL	60		MCG/DL	40 - 150	
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	57		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	158 H		MG/DL	LESS THAN 130	

>> REPORT CONTINUED ON NEXT PAGE <<

1/2/91

INDICATES TESTING SITE SEE REVERSE SIDE †

Clinical Laboratories

ACCT. NO. 2541

LAB NO. 2855913 PAGE 1

DATE COLLECTED 10/17/90

PES-FLORIDA INC
444 S MILITARY TRAIL S-590
DELRAY BEACH, FL 33484

TIME COLLECTED 9AM AGE 50 SEX F
DATE ENTERED 10/17/90
DATE REPORTED 10/18/90 8:00AM
REPORT STATUS FINAL

** CONFIDENTIAL REPORT **
EA 00 ROUTE W3 STOP 160
MMENTS: "FASTING SPECIMEN"

10179015451/829322P

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
CHEMZYME PLUS/CBC/UA					
CHEMZYME					MI
GLUCOSE	94		MG/DL	70 - 115	
SODIUM	143		MEQ/L	135-148	
POTASSIUM	4.7		MEQ/L	3.5-5.3	
CHLORIDE	105		MEQ/L	95-110	
CARBON DIOXIDE CONTENT	25		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	13			5-15	
UREA NITROGEN	15		MG/DL	7-25	
CREATININE	0.9		MG/DL	0.7-1.4	
BUN/CREATININE RATIO	17			8-20	
URIC ACID	2.6		MG/DL	2.5 - 7.5	
CALCIUM	9.6		MG/DL	8.5-10.6	
PHOSPHORUS, INORGANIC	3.5		MG/DL	2.5-4.5	
PROTEIN, TOTAL	7.0		GM/DL	6.0-8.5	
ALBUMIN	4.3		GM/DL	3.2-5.5	
GLOBULIN, TOTAL	2.7		GM/DL	1.5-3.8	
A/G RATIO	1.6			1.1-2.2	
CALCIUM, IONIZED	4.3		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.3		MG/DL	0.2-1.2	
ALK PHOS, TOTAL	74		U/L	20 - 140	
LACTATE DEHYDROGENASE	150		U/L	0 - 250	
AST (SGOT)	18		U/L	0-50	
ALT (SGPT)	14		U/L	0 - 55	
[redacted]	[redacted]		MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE [redacted] 20 YEARS OLD OR GREATER.					
TRIGLYCERIDES	70		MG/DL	20-160	
IRON, TOTAL	72		MCG/DL	40 - 150	
COMPLETE BLOOD CT & DIFF					MI
WHITE BLOOD CELLS	5.1		THOUSAND/CU.MM.	3.8 - 10.8	
RED BLOOD CELLS	4.22		MILLIONS/CU.MM.	3.90 - 5.20	
HEMOGLOBIN (B)	12.3		GM/DL	12.0 - 15.6	
HEMATOCRIT	37.8		%	35.0 - 46.0	
MCV	89.5		FEMTOLITERS	80.0 - 100.0	
MCH	29.3		PICOGRAMS	27.0 - 33.0	
MCHC	32.7		%	32.0 - 36.0	
RDW	11.5		UNITS	10.0 - 15.0	
PLATELET COUNT	245		THOUSAND/CU.MM.	130 - 400	
NEUTROPHILS	62		%	40 - 75	
NEUTROPHILS, ABSOLUTE	3.15		THOUSAND/CU.MM.	1.52 - 8.10	
LYMPHOCYTES	30		%	18 - 42	
LYMPHOCYTES, ABSOLUTE	1.51		THOUSAND/CU.MM.	0.68 - 5.07	
MONOCYTES	6		%	0 - 10	
MONOCYTES, ABSOLUTE	0.29		THOUSAND/CU.MM.	0.10 - 1.08	
EOSINOPHILS	2		%	0 - 6	

>> REPORT CONTINUED ON NEXT PAGE <<

INDICATES TESTING SITE SEE REVERSE SIDE

SB Clinical Laboratories

ACCT. NO. 25411

[redacted]

PAGE 1

LAB NO. 2955884
DATE COLLECTED 10/22/90
TIME COLLECTED 0900 AGE 50 SEX F
DATE ENTERED 10/22/90
DATE REPORTED 10/23/90 5:22AM
REPORT STATUS FINAL
10229011055/845119P

S-FLORIDA INC
244 S MILITARY TRAIL S-590
AY BEACH, FL 33484

CONFIDENTIAL REPORT **
00 ROUTE W3 STOP 160
MENTS: FAST

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
A.R.E. PANEL #2					
CHOLESTEROL, TOTAL	[redacted]		MG/DL	LESS THAN 200	MI
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	115		MG/DL	20-160	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	48 L		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	214 H		MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	5.94				

****
CORONARY HEART DISEASE RISK TABLE

	RELATIVE RISK	T/HDL CHOL RATIO
MEN	0.5 AVERAGE	3.43
	AVERAGE	4.97
	2 X AVERAGE	9.55
	3 X AVERAGE	23.39
WOMEN	0.5 AVERAGE	3.27
	AVERAGE	4.44
	2 X AVERAGE	7.05
	3 X AVERAGE	11.04

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>> END OF REPORT <<

INDICATES TESTING SITE SEE REVERSE SIDE

Clinical Laboratories

[redacted]

ACCT. NO. 25411

ES-FLORIDA, INC
1 S MILITARY TRAIL S-590
AY BEACH, FL 33484

LAB NO. 2955824 PAGE 1

[redacted] 10/26/90

TIME COLLECTED 0830 AGE 50 SEX F

DATE ENTERED 10/26/90

DATE REPORTED 10/29/90 5:42AM

REPORT STATUS FINAL

10269011414/868655F

* CONFIDENTIAL REPORT **

EA 00 ROUTE W3 STOP 160

OMMENTS: FASTING

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
A.R.E. PANEL #2					
[redacted]			MG/DL	LESS THAN 200 MI	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	108		MG/DL	20-160	MI
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	46 L		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45					
FEMALE GREATER THAN 55					
LDL CHOLESTEROL	213 H		MG/DL	LESS THAN 130	
CHOLESTEROL/HDL RATIO	6.11				
**********					
CORONARY HEART DISEASE RISK TABLE					
RELATIVE RISK	T/HDL CHOL RATIO				
MEN 0.5 AVERAGE	3.43				
AVERAGE	4.97				
2 X AVERAGE	9.55				
3 X AVERAGE	23.39				
WOMEN 0.5 AVERAGE	3.27				
AVERAGE	4.44				
2 X AVERAGE	7.05				
3 X AVERAGE	16.81				
**********					
>> END OF REPORT <<					

INDICATES TESTING SITE SEE REVERSE

SD Clinical Laboratories

[redacted]

ACCT. NO. 25411

LAB NO. 2956010 PAGE 1

ES-FLORIDA INC
6244 S MILITARY TRAIL S-590
RAY BEACH, FL 33484

[redacted]

TIME COLLECTED 1020 AGE 50 SEX F
DATE ENTERED 12/28/90 26
DATE REPORTED 12/31/90 5:32AM
REPORT STATUS FINAL

* CONFIDENTIAL REPORT **
00 ROUTE W3 STOP 160
IMENTS:

1228901258J/233217U

TEST	RESULT	OUT OF RANGE (OR INTERPRETATION)	UNITS	REFERENCE RANGE	SC
HEMZYME PLUS/CBC+/UA					
CHEMZYME					MI
GLUCOSE	97		MG/DL	70 - 115	
SODIUM	142		MEQ/L	135 - 148	
POTASSIUM	4.9		MEQ/L	3.5 - 5.3	
CHLORIDE	104		MEQ/L	95 - 110	
CARBON DIOXIDE CONTENT	26		MEQ/L	24 - 32	
ELECTROLYTE BALANCE	12			5-15	
UREA NITROGEN	15		MG/DL	7 - 25	
CREATININE	1.0		MG/DL	0.7 - 1.4	
BUN/CREATININE RATIO	15			8-20	
URIC ACID	2.7		MG/DL	2.5 - 7.5	
CALCIUM	9.1		MG/DL	8.5 - 10.6	
PHOSPHORUS, INORGANIC	3.1		MG/DL	2.5-4.5	
PROTEIN, TOTAL	6.9		GM/DL	6.0-8.5	
ALBUMIN	4.1		GM/DL	3.2-5.5	
GLOBULIN, TOTAL	2.8		GM/DL	1.5-3.8	
A/G RATIO	1.5			1.1-2.2	
CALCIUM, IONIZED	4.1		MG/DL	3.8-4.8	
BILIRUBIN, TOTAL	0.3		MG/DL	0.2 - 1.2	
ALK PHOS, TOTAL	75		U/L	20 - 140	
LACTATE DEHYDROGENASE	206		U/L	0 - 250	
AST (SGOT)	25		U/L	0-50	
ALT (SGPT)	19		U/L	0 - 55	
[redacted]	[redacted]	[redacted]	MG/DL	LESS THAN 200	
200 - 239 MG/DL IS BORDERLINE HIGH FOR 20 YEARS OLD OR GREATER					
TRIGLYCERIDES	95		MG/DL	20-160	
IRON, TOTAL	82		MCG/DL	40 - 150	
					MI
CHOLESTEROL, HIGH DENSITY LIPOPROTEIN	59		MG/DL		
DESIRABLE LEVELS OF HDL CHOLESTEROL ARE: MALE GREATER THAN 45 FEMALE GREATER THAN 55					
LDL CHOLESTEROL	211 H		MG/DL	LESS THAN 130	
>> REPORT CONTINUED ON NEXT PAGE <<					

1/4/91

INDICATES TESTING SITE SEE REVERSE SIDE †

Exhibit A

acid to the body during times of peak lipid production or synthesis.

Furthermore, because the composition is orally administered prior to sleep, larger amounts of the active ingredient nicotinic acid is available during lipid synthesis times than if the composition is administered during hours when the patient is awake, i.e., in the morning or afternoon hours. Hence, less nicotinic acid may be required to be administered than would otherwise be required with compositions heretofore known in the art, while achieving substantially similar or even superior antihyperlipidemia results for at least one or more of the lipoproteins or particles discussed above. Because less nicotinic acid is administered and because the invention specifically describes once a day dosing, there is a lesser amount of the side effects as discussed hereinabove. The time release sustaining compositions according to the present invention ensure that effective antihyperlipidemia amounts of nicotinic acid are released to the patient during times of lipid production.

General Experimental

In order to demonstrate the effectiveness of the compositions and method of the present invention over known antihyperlipidemia compositions and methods heretofore known in the art, a number of substantially identical composition were prepared according to the disclosure hereinabove. The composition ingredients and amounts are listed in TABLE I hereinbelow.

TABLE I
Test Tablet Composition

Ingredient	375 mg	500 mg	750 mg
Nicotinic Acid	375.0	500.0	750.0
Hyroxypropyl methylcellulose	188.7	203.0	204.7
Povidone	12.9	17.2	25.9
Stearic Acid	5.8	7.3	9.9
TOTAL	582.4 mg	727.5 mg	990.5 mg